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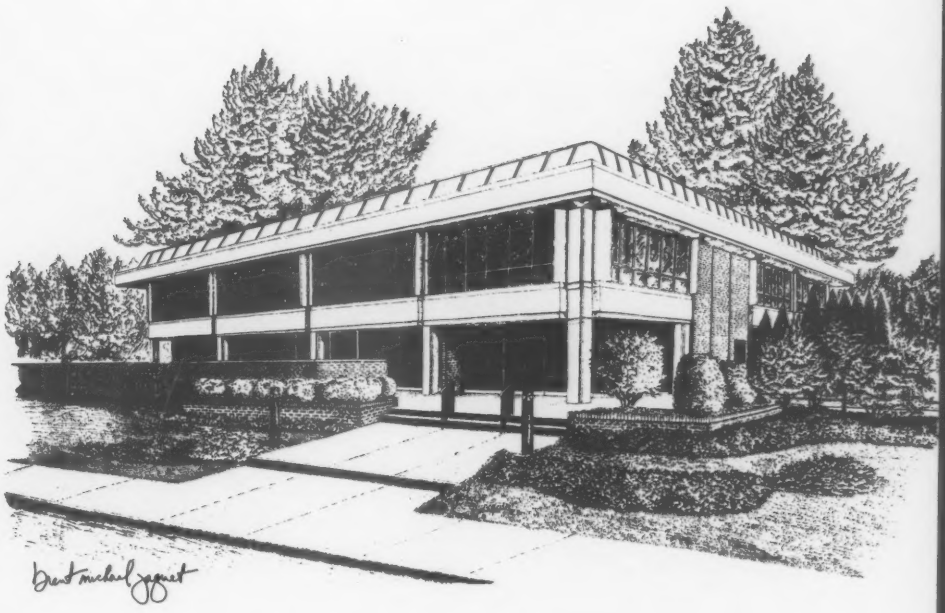

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1555 ANNOUNCEMENTS

Metabolic Studies of Delta-9-Tetrahydrocannabinol in Cancer Patients[1]

Stephen Frytak,* Charles G. Moertel, and Joseph Rubin[2,3]

The metabolism of oral delta-9-tetrahydrocannabinol (THC) was studied in nine patients with gastrointestinal neoplasms receiving chemotherapy regimens containing 5-FU and semustine. Plasma levels of THC and its metabolites 11-OH-delta-9-THC (11-OH-THC) and 11-*nor*-9-carboxy-delta-9-THC (C-THC) were measured. Plasma levels of THC and its metabolites were quite variable among the patients studied. Plasma levels of THC and 11-OH-THC tended to peak at the same time; the C-THC levels peaked later and lasted much longer than the others. Mean half-lives of THC, 11-OH-THC, and C-THC were estimated to be 1.5, 2.1, and 4.4 hours, respectively. Multiple doses of THC did not produce a significant additive effect on the plasma concentrations of the biologically active metabolites THC and 11-OH-THC. No correlation between antiemetic effect or cannabinoid toxicity and plasma levels of the three metabolites could be made in this small number of patients. [Cancer Treat Rep 68:1427–1431, 1984]

The use of delta-9-tetrahydrocannabinol (THC) in the care of cancer patients is a commonly encountered topic in current oncologic literature. Antiemetic, analgesic, and appetite-stimulating properties have been attributed to THC by many investigators (1–5). Although cannabis preparations have been used for centuries, only within the last few years have high-quality synthetic preparations and reproducible assay techniques become available to study the metabolism of these compounds. Figure 1 depicts the presumptive major metabolic pathways of THC and the biologic activity of the various metabolites, based on our present knowledge (6). Most of the early studies with THC, the major psychoactive component of marijuana, have been in young, healthy volunteers, many with previous marijuana exposure. Metabolic studies of oral THC in tumor patients are quite limited considering the amount of attention recently given to the use of this agent in the supportive care of cancer patients. Our investigation focused on the study of oral THC metabolism in patients with tumor.

MATERIALS AND METHODS

Nine patients (mean age, 54 years) receiving 5-FU/semustine therapy for various gastrointestinal malignancies were given oral THC, and serial plasma samples were drawn to study its metabolism. The THC was a standard sesame oil preparation (provided by the National Institute of Drug Abuse) placed in a standard gelatin capsule. Preliminary results of these findings were published previously as part of a large antiemetic study (3). Plasma THC, 11-OH-delta-9-THC (11-OH-THC), and 11-*nor*-9-carboxy-delta-9-THC (C-THC) were measured at various intervals. Analysis of the plasma samples was done by Battelle Laboratories, Columbus, OH, using a gas chromatographic-chemical ionization-mass spectrophotometric technique (7). Under ideal conditions, this system has the capability to measure THC concentrations as low as 0.2 ng/ml. The assay precision for the analysis of plasma samples containing a known amount of THC was as follows: at 0.92, 4.6, and 18.4 ng/ml, the mean measured concentrations and standard deviations (ng/ml) were 0.88 ± 0.39, 4.75 ± 0.89, and 18.85 ± 0.45, respectively. In our study, the minimum plasma THC concentration specified was 1 ng/ml. The analytic procedure for the 11-OH-THC and C-THC metabolites had not been utilized as extensively as that for THC and therefore was not as thoroughly validated. The assay precision for the analysis of plasma samples containing a known amount of 11-OH-THC or C-THC was as follows: at 1, 10, and 100 ng/ml of 11-OH-THC, the relative standard deviations were 7%, 2%, and 3%, respectively; at 1, 10, and 100 ng/ml of C-

[1]Received June 16, 1981; revised Jan 28, 1983; accepted June 26, 1984.

[2]Mayo Clinic, Rochester, MN.

[3]We thank Mr. Bruce Hidy, Battelle Laboratories, Columbus, OH, and Dr. Richard L. Hawks, National Institute of Drug Abuse, for their advice and assistance.

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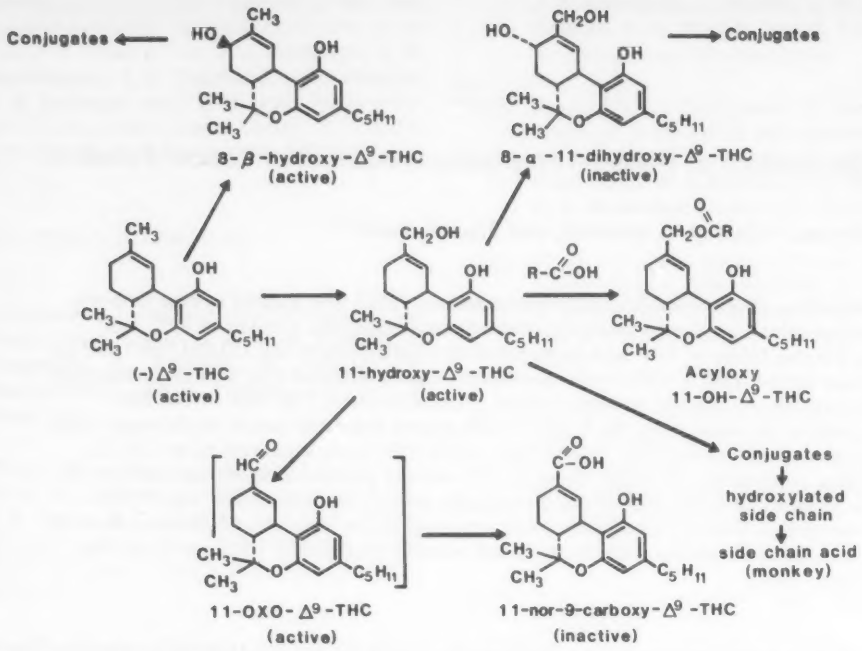

FIGURE 1.—Metabolic pathways of THC (*from* ref 6; reproduced with permission of the author and copyright owner).

THC, the relative standard deviations were 31%, 2%, and 2%, respectively. Plasma half-lives of THC, 11-OH-THC, and C-THC were obtained by nonlinear least squares regression analysis when there were three or more points on the decay curve after the peak plasma concentration had been obtained.

Six patients, three with biopsy-proven liver metastasis and three without hepatic involvement, were given 15 mg of oral THC 2 hours prior to the initiation of their chemotherapy. Three other patients without liver metastasis were given 15 mg of oral THC 2 hours prior to initiation of their chemotherapy and 2 and 8 hours after chemotherapy. The patients were not previous marijuana users. Characteristics of these nine patients are shown in table 1.

RESULTS

Figure 2 illustrates the plasma levels of THC, 11-OH-THC, and C-THC at selected intervals over a 24-hour period in patients with gastrointestinal neoplasms receiving one 15-mg oral dose of THC. In the six patients receiving one oral dose of THC, there was a wide range of peak plasma levels of the three metabolites, with variable

TABLE 1.—Patient characteristics

Patient	Age (yrs)/ sex	Primary tumor	Liver metastases	No. of THC doses	Smoker*	Alcohol*	Comments
1	53/F	Gallbladder	Yes	1	++	+	Direct bilirubin, 15 mg/dl; prior aspirin with codeine
2	51/F	Stomach	Yes	1	-	++	No gastric surgery, normal liver functions
3	47/M	Stomach	No	1	-	+	Total gastrectomy, 4 weeks' pretreatment; vitamin B_{12}
4	70/F	Stomach	No	1	-	-	Total gastrectomy, 5 years' pretreatment; vitamin B_{12} thiazide diuretic
5	55/M	Colon	Yes	1	-	+++	Normal liver functions; digoxin, quinidine, acetaminophen
6	41/M	Colon	No	1	-	+	L-triiodothyronine
7	54/M	Stomach	No	3	-	+	Subtotal gastrectomy; 6 weeks' pretreatment
8	61/M	Colon	No	3	++	++	
9	58/m	Colon	No	3	-	++	

* - to ++++.

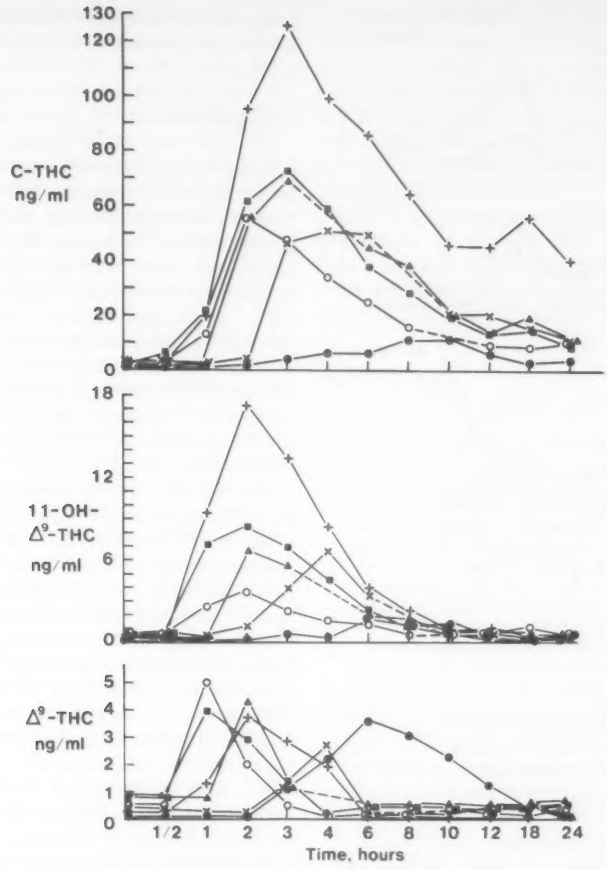

FIGURE 2.—Plasma levels of THC, 11-OH-THC, and C-THC in 6 patients with gastrointestinal neoplasms receiving one 15-mg oral dose of THC. The times shown on the abscissa are points at which plasma levels for THC and its metabolites were drawn. ● = Patient 1; + = Patient 2; × = Patient 3; ○ = Patient 4; ■ = Patient 5; and ▲ = Patient 6.

times at which the peak levels occurred. Median (mean) peak plasma levels (ng/ml) for THC, 11-OH-THC, and C-THC were 3.65 (3.9), 6.65 (7.4), and 62.5 (54.5), respectively. Median times (hours) of peak plasma levels for these three compounds after administration of oral THC were 2, 2, and 3, respectively. For most patients, THC was not detectable in the plasma 6 hours after administration. Only Patient 1 with severe liver metastasis had detectable plasma levels of THC at 12 hours. C-THC levels were consistently detectable at 24 hours.

Figures 3 and 4 illustrate the plasma levels of the THC metabolites in the three patients receiving multiple doses of oral THC. Peak plasma levels (ng/ml) of THC, 11-OH-THC, and C-THC ranged from 3.6 to 6.3, from 8.6 to 15.6, and from 98.2 to 203, respectively. Median times (hours) of peak plasma levels from THC, 11-OH-THC, and C-THC were 1, 2, and 8, respectively. There did not appear to be any major additive effect on the plasma concentration of THC or 11-OH-THC when multiple doses of THC were utilized. In most instances, the 24-hour plasma levels of C-THC were higher following the multiple-dose schedule compared to those seen after the single-dose technique. There were only three plasma samples taken for analysis of these THC metabolites during the period from 12 to 24 hours (broken lines on graph). Thus, the graphs depict only a rough outline of the plasma values of the metabolites during this period (interval following the third THC dose). The samples at 18 and 24 hours, however, supply information regarding any possible accumulation of the various metabolites in the blood.

As a secondary measure, we assessed emesis and drug toxicity during the study. Only one patient (No. 4) vom-

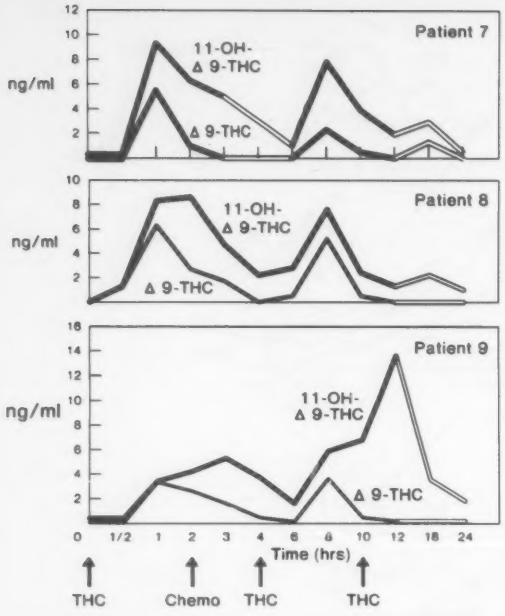

FIGURE 3.—Plasma levels of THC and 11-OH-THC in 3 patients with gastrointestinal neoplasms receiving 15 mg of oral THC.

ited during the study. Although this patient had a total gastrectomy, she achieved one of the higher THC plasma levels and experienced mild sedation from a single dose of THC. This patient also had one of the lowest 11-OH-THC levels recorded.

Side effects from the THC were noted in six (Nos. 1, 2, 4, 6, 7, and 9) of nine patients. A "high," defined as a mood change consisting of a tendency to laugh, elation, heightened awareness, mild aberrations of fine motor coordination, or minimal distortion of activities and interactions with others, was noted in two patients (Nos. 7 and 9) (1).

DISCUSSION

There was considerable variation in the peak plasma levels of THC and its metabolites among the patients. This is consistent with the previously reported erratic gastrointestinal absorption of oral THC (8). There were insufficient points with measurable THC concentration to obtain an accurate and complete pharmacokinetic profile for all patients. However, it was possible to estimate the mean half-life for the elimination of plasma THC in five patients: 1.5 hours (range, 0.2-3.6). The mean half-life for the elimination of plasma 11-OH-THC in eight patients was 2.1 hours (range, 1.2-3.1), and the mean half-life for the elimination of C-THC in nine patients was 4.4 hours (range, 2.6-10.8).

Plasma levels of THC obtained in our study were similar to those obtained by Chang et al (9) in an antiemetic study of THC given orally at a dose of 10 mg/m^2 to patients receiving cyclophosphamide and doxorubicin as adjuvant treatment for a surgically resected sarcoma. The method used for analyzing the plasma samples of THC in Chang's study and ours was identical, and both were performed in the same laboratory. In a previous antiemetic study by Chang et al (2), in which they utilized the same THC dosage and schedule (9) in young adults receiving high-dose methotrexate as adjuvant treatment for osteogenic sarcoma, the plasma THC levels were approximately two to three times higher. The reasons for this discrepancy in plasma THC levels in the two studies by Chang et al are not obvious.

To our knowledge, only one other study looked at the plasma levels of THC, 11-OH-THC, and C-THC using a gas chromatographic/mass spectrophotometric tech-

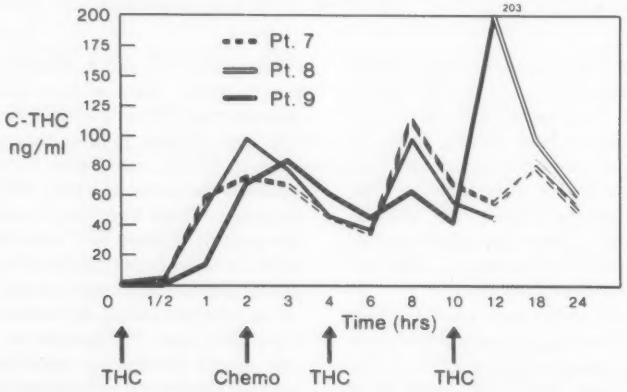

FIGURE 4.—Plasma levels of C-THC in 3 patients with gastrointestinal neoplasms receiving 15 mg of oral THC, 3 times daily.

nique. This was the study of Wall and Brine (10), in which male volunteers who were experienced marijuana users were given 4–5 mg of iv THC. In this study, the THC levels were 50–60 ng/ml in 10 minutes and tapered off thereafter. Peak levels of only 2–3 ng/ml of 11-OH-THC were found at approximately 30 minutes after THC injection. Levels of the active metabolite 11-OH-THC were consistently two to three times higher than those of THC in our study after THC was administered orally. Conceivably, the slower absorption of THC when given orally may permit greater extraction of it by the liver, with subsequently more abundant formation of 11-OH-THC.

Ohlsson et al (11), in their study of 11 experienced marijuana users between 18 and 35 years of age who ingested a chocolate cookie containing 20 mg of THC, noted maximal mean values of THC between 5 and 6 ng/ml usually 60–90 minutes after ingestion. In Ohlsson's study as well as ours, the plasma levels of THC at 6 hours were $\leqslant$ 1 ng/ml. If there is any strong relationship between plasma levels of THC and antiemetic effect, it would seem that THC dosage should be repeated within a 6-hour interval. Although Ohlsson's study differed markedly from ours in the patient populations and dosages used, the plasma values of THC were comparable.

Various gastrointestinal surgical procedures including total gastrectomy did not seem to substantially alter the absorption of THC as reflected in its plasma levels. Likewise, cigarette smoking, alcohol intake, and the use of other medicinals did not seem to affect the overall metabolism of THC.

Extensive liver metastasis, sufficient to raise the serum bilirubin substantially, altered the metabolism of THC. Patient 1 with marked jaundice (direct bilirubin, 15 mg/dl) had a delayed peak plasma level of THC with an uncharacteristically slow disappearance rate. Extremely low 11-OH-THC and C-THC plasma levels were noted in this patient, which is consistent with the known hepatic metabolism of THC. Sedation was also very prominent in this patient. Liver metastasis of a lesser degree, as illustrated in the other two patients with hepatic involvement, did not substantially affect the metabolism of THC.

Because of the small number of patients in our study, no meaningful correlation between plasma levels of either THC or 11-OH-THC and antiemetic effect can be substantiated. Conflicting results on this matter have been reported previously (2). Despite rather wide variations in plasma THC levels, only one patient experienced nausea and vomiting. This patient had a relatively high plasma level of THC. Other patients with much lower THC levels did not experience emesis. The patient who experienced vomiting in this study had a relatively lower 11-OH-THC level than the other patients. 11-OH-THC is pharmacologically active and has been postulated to be responsible for some of the physiologic effects attributed to THC (12). A much larger population of patients would need to be studied in order to determine if indeed there is a correlation between plasma levels of THC or its metabolites and antiemetic effect.

Reliable technology is now available to investigate the metabolism of cannabinoids. A concentrated effort should be made to study them in cancer patients using trials designed to correlate therapeutic and toxic properties with their pharmacokinetic behavior.

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Cisplatin-MECY (Methotrexate-Leucovorin Rescue Plus Cyclophosphamide) Versus Cisplatin-CHAD (Cyclophosphamide, Hexamethylmelamine, Doxorubicin, and Cisplatin) As Initial Chemotherapy in Stage III–IV Ovarian Adenocarcinoma[1]

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Thirty-three patients with advanced-stage ovarian adenocarcinomas, with no prior chemotherapy, were treated with weekly cisplatin (DDP) for four courses followed by five monthly courses of one of two randomly assigned multidrug combinations. These combinations were high-dose methotrexate-leucovorin plus cyclophosphamide (MECY) or cyclophosphamide, hexamethylmelamine, doxorubicin, and DDP (CHAD). Patients with no clinically measurable disease after 6 months of therapy were evaluated by laparoscopy. In the absence of disease progression at the time of the laparoscopy the study design called for a repeat cycle of four weekly DDP courses and another five monthly courses of the assigned multidrug combination. All patients with no evidence of disease after 1 year of treatment had a second-look laparoscopy which, if negative, was followed by a second-look laparotomy. This report includes all of the consecutively entered patients observed for a minimum of 1 year or to death. DDP-MECY and DDP-CHAD were similarly active for overall response rates and complete response rates according to laparoscopic criteria. However, DDP-MECY had a statistically significantly lower relapse rate ($P < 0.02$) and a statistically significantly higher negative second-look laparotomy rate than did DDP-CHAD. Using all entered patients, with no exclusions from analysis, eight of 17 patients (47%) treated with DDP-MECY had negative second-looks after 1 year of treatment. This compares with one of 16 (6%) negative second-looks in patients treated with DDP-CHAD ($P < 0.02$). The high negative second-look rate with DDP-MECY is exciting. Positive cytologic washings at the 6-month laparoscopic evaluation were highly predictive that residual disease would be found at the 1-year second-look surgery. Only one patient with positive peritoneal cytology after 6 months of treatment was found to have a negative second-look after 1 year of therapy. [Cancer Treat Rep 68:1433–1438, 1984]

Cisplatin (DDP), alone or in combination with other chemotherapeutic agents, has proved to be highly active against ovarian adenocarcinoma. For the most part, DDP has been used in combination regimens with other active agents. However, it has also been effective by itself as primary chemotherapy and as second-line therapy with response rates ranging between 26.5% and 31% (1–4).

In all of the studies cited above, DDP was administered at 3–4-week intervals between courses. Recently, we reported high activity (70%) with a regimen of *weekly* DDP as *third-line* chemotherapy in patients with stage III–IV epithelial ovarian cancers (5). Our experience with weekly DDP was remarkably better than our experience with DDP given as third-line therapy with 3–4-week intervals between courses (5%) (6).

Ovarian adenocarcinoma is one of the most chemotherapy-responsive of all solid tumors. However, despite initial high response rates, the 5-year survival rate is substantially < 10%. The explanation for this seeming paradox is the high relapse rate. Relapse is generally considered to be due to the emergence of resistant tumor which was either present initially or developed during treatment. The rationale behind multidrug and/or alternating drug regimens is to delay or prevent the development of resistance.

The present paper presents our results with a type of

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alternating regimen consisting of four *weekly* DDP courses followed by monthly courses of one of two randomly assigned proven active multidrug regimens: high-dose methotrexate-leucovorin rescue plus cyclophosphamide (MECY) (7) or cyclophosphamide, hexamethylmelamine, doxorubicin, and DDP (CHAD) (8).

A partial report on the efficacy of weekly DDP alone as initial chemotherapy in this disease has been published (9).

MATERIALS AND METHODS

All patients had histologically proven primary ovarian adenocarcinomas which were International Federation of Gynecology and Obstetrics (FIGO) stage III or IV. None had received prior chemotherapy. The patients were stratified according to some of the factors listed in table 1 and were randomized to receive either DDP-MECY or DDP-CHAD. Both groups received four weekly courses of DDP followed by five monthly courses of the randomly assigned multidrug regimen beginning 3-4 weeks after the fourth course of DDP.

Because of more aggressive initial surgical treatment and because of high response rates to the chemotherapeutic regimens, few patients had clinically measurable disease after the first 2-3 months of treatment. Therefore, it was felt that the usual clinical criteria of response were inappropriate and inadequate in the face of such high rates of tumor response. For this reason, an interim evaluation with laparoscopy after 6 months of therapy was incorporated in the study.

All patients who had no clinically measurable disease after 6 months of therapy were evaluated by laparoscopic criteria. A complete laparoscopic response was defined as *no* evidence of macroscopic tumor, *negative* biopsies from any suspicious areas, and *negative cytologic washings* (from pelvis and both paracolic gutters). A partial laparoscopic response was defined as ranging between a > 50% reduction in tumor remaining after original surgery to no macroscopic tumor with negative biopsies, but *positive cytology* on washings; ie, positive cytology as the only evidence of residual disease was considered a partial response. In the absence of disease progression, the study design called for another cycle of four weekly DDP courses followed by another five monthly courses of combination of therapy.

All patients who, after 1 year of treatment, showed no evidence of disease had a second-look laparoscopy which, if negative, was followed by a second-look laparotomy. The chemotherapy was stopped in patients with negative second-look laparotomies and the patients were then closely followed in the clinic. A negative second-look laparotomy consisted of no macroscopic tumor, negative biopsies from suspicious and previously known tumor sites, and negative cytologic washings from the pelvis and both paracolic gutters.

The patients included in the present report are all of the eligible patients consecutively randomized and observed for a minimum of 1 year or to death.

Chemotherapeutic Regimens

DDP.—The dose was 1 mg/kg/week for 4 weeks. DDP was given iv over a 4-hour period with 3-6 hours of pre- and post-treatment iv hydration and with mannitol and lasix diuresis and potassium replacement.

MECY.—Methotrexate (750 mg/m^2 iv) was given as a 4-hour infusion. Six hours after the completion of the methotrexate, leucovorin "rescue" was begun with 10 mg/m^2 im every 6 hours for 12 doses. In addition, cyclophosphamide was given iv at a dose of 250 mg/m^2/day for 5 days. Supplemental iv hydration was carried out for 5 days. During the first 48 hours sodium bicarbonate was given to alkalinize the urine (7). Courses were repeated every 4 weeks.

CHAD.—Cyclophosphamide (400 mg/m^2), doxorubicin (25 mg/m^2), and DDP (50 mg/m^2) were given iv on Day 1. The pre- and post-hydration and diuretic program was the same as that described for the DDP regimen. Hexamethylmelamine at a dose of 150 mg/m^2 was given orally on Days 8-21. Pyridoxine (100 mg 3 times a day) was also given on Days 8-21. Courses were repeated every 4 weeks (8).

Statistical analyses were done by means of Fisher's exact test.

RESULTS

Comparability

The patient characteristics of the two chemotherapy treatment groups are compared in table 1. The groups were well-matched for factors thought to influence chemotherapeutic response and survival.

Response to Treatment

The therapeutic results are shown in table 2. Thirty-three patients were entered in the study, with random allocation to each combination drug regimen.

All response data are based on laparoscopy findings. The laparoscopic response criteria are more rigorous than the usual clinical criteria and are defined in the Materials and Methods section.

Two patients in the DDP-MECY group and three in the DDP-CHAD group were not evaluable for response because of either poor visualization at laparoscopy or because laparoscopy was not done because patients were known to have extensive adhesions present at the time of their original surgery. These patients became evaluable later by second-look laparotomies.

Two patients, randomized to receive MECY, had what

TABLE 1.—Characteristics of patients treated with DDP-MECY or DDP-CHAD regimens*

Characteristic	Treatment group	
	DDP-MECY	DDP-CHAD
Total	17	16
Mean age in yrs (range)	59.4 (32-75)	58.8 (20-74)
FIGO stage		
III	9	11
IV	8	5
Histology		
Serous	9	11
Mucinous		
Undifferentiated	6	5
Other	2	—
Histologic differentiation		
Well	1	1
Moderate	6	6
Poor	10	9
Surgery		
Biopsy only	5	3
Tumor-reductive	12	12
Unknown	—	1
Residual tumor after surgery		
⩾ 2 cm	10	9
< 2 cm	6	6
Unknown	1	1

* Unless specified otherwise, values = No. of patients.

appeared to be sensitivity reactions to DDP, with elevations in serum creatinine and BUN and decreased creatinine clearance after their first course of DDP. Renal function returned to normal but no more DDP was given. Even though these patients subsequently received only MECY and did not have the potential benefit of further DDP, they were not excluded from analysis. Of these two patients, one had progressive tumor growth and died 3 months after starting treatment. The other patient had an initial partial response but relapsed after 15 months of MECY therapy.

The overall response rates for DDP-MECY and DDP-CHAD were 80% and 92%, respectively; the complete response rates were 47% and 46%, respectively. Three patients, all of whom were in the DDP-MECY group, showed tumor progression clinically and did not require laparoscopy. One patient treated with DDP-CHAD had stable disease by laparoscopy. The median duration of response in the DDP-MECY group has not yet been reached but will be > 16 months, with a present range of 8-33 months. The median duration of response in the DDP-CHAD group is only 12 months, with a range of 6-21 months. The duration of response was measured from the day chemotherapy was started.

Significant differences were seen in the failure to respond plus relapse rates between these two chemotherapeutic programs. Patients were considered to be in this category, which comprised all failures, whether they had had an initial response followed by recurrence or if they had failed to respond initially. Nine of 17 patients (53%) allocated to receive treatment with DDP-MECY and 15 of 16 (94%) treated with DDP-CHAD either failed to respond or relapsed. These differences are statistically significant ($P < 0.02$). Statistical calculations were based on the number of patients entered, with no exclusions.

Another statistically significant difference between the two regimens is seen when one compares the two groups for negative second-look laparotomies. To be eligible for a second-look laparotomy the patients had to have been treated with chemotherapy for approximately 1 year and have no clinical evidence of disease. Within the DDP-MECY group there were 11 patients who were eligible for second-look procedures; there were ten eligible patients in the DDP-CHAD group. Eight of 11 second-look procedures in the DDP-MECY group were negative; only one of ten similar procedures was negative in the DDP-CHAD group. Nearly one-half of the patients (47%; eight of 17) randomized to receive DDP-MECY had negative second-look laparotomies. This is in sharp contrast to the DDP-CHAD-treated patients (6%; one of 16). The difference is statistically significant ($P < 0.02$).

Of the eight DDP-MECY-treated patients who had negative second-looks, the median duration since the negative second-look and cessation of chemotherapy is 9 months, with a range of 2-21 months. Only one patient in this group has shown recurrent disease; she had stage IV disease with peritoneal tumor and a biopsy-positive left supraclavicular node. With treatment the left supraclavicular node disappeared and the interim laparoscopy was negative. Second-look procedures included a retroperitoneal dissection with node biopsies, all of which were negative after 1 year of treatment. The left supra-

TABLE 2.—Results of randomized trial: DDP-MECY vs DDP-CHAD in the treatment of stage III-IV ovarian adenocarcinoma: laparoscopy and laparotomy criteria*

	Treatment group	
	DDP-MECY	DDP-CHAD
Total	17	16
Nonevaluable for response	2 (1,† 1‡)	3 (2,† 1‡)
Evaluable for response	15	13
Total No. of responders	12 (80%)	12 (92%)
Complete response	7 (47%)	6 (46%)
Partial response	5 (33%)	6 (46%)
Stable disease	—	1
Disease progression	3	—
Median duration of response in mos (range)	16+ (8-33)	12 (6-21)
Failure to respond + relapse rate	9 (53%)	15 (94%) $P = < 0.02$
NED§ at second-look laparotomy	8 (47%)	1 (6%) $P = < 0.02$

* Unless otherwise specified, values = No. of patients.
† Unsatisfactory visualization at laparoscopy.
‡ Laparoscopy not done.
§ NED = no evidence of disease.

clavicular node lesion recurred 3 months after second-look. External-beam radiotherapy was delivered to the left supraclavicular area. The node disappeared and she has had no evidence of disease for 13 months. The one patient who had a negative second-look after treatment with DDP-CHAD has shown no evidence of disease without therapy for 12 months.

Toxicity

Almost all patients had mild to moderate nausea and vomiting. Severe vomiting, when it occurred, was more frequent in the CHAD group. Alopecia was usually mild with MECY and nearly always marked with CHAD.

Table 3 shows some of the other more severe toxic reactions. Only two patients, who received MECY, had transient severe bone marrow depression. Two patients had transient mild mouth soreness, but there were no ulcerations or mucositis. Two patients had renal insufficiency after their first course of weekly DDP. Both patients had been randomized to receive DDP-MECY. They each had serum creatinine levels > 2.0 mg/dl, elevations of BUN, and abnormally low creatinine clearances. The reactions occurred despite adequate hydration and seemed more idiosyncratic than toxic. The kidney function tests reverted to normal, but weekly DDP was discontinued and further therapy was with MECY alone.

Most of the observed toxicity was neurotoxicity in patients receiving DDP-CHAD. The relatively frequent neurotoxicity observed with CHAD probably reflected the additive effects of DDP and hexamethylmelamine. Four patients had mild paresthesias of fingers and toes.

TABLE 3.—Toxic reactions to chemotherapeutic regimens*

	Treatment group	
	DDP-MECY	DDP-CHAD
Evaluable	17	16
Severe leukopenia (< 1000 cells/mm^3)	2	—
Severe thrombocytopenia (< 50,000 cells/mm^3)	2	—
Oral ulcerations	—	—
Renal insufficiency (serum creatinine > 2.0 mg/dl)	2	—
Numbness and tingling (mild)	—	4
Numbness and tingling with impaired function of hands and/or feet	—	6
Depressed or absent deep tendon reflexes	—	4
Impaired hearing	—	1
Decreased left ventricular ejection fraction (< 40%)	—	1
Chemotherapy-related death	—	—

* Values = No. of patients.

In one patient this was observed during weekly DDP courses alone; in the other three patients these symptoms began after starting CHAD. Another six patients developed severe neurotoxicity at completion, or near completion, of planned courses of CHAD. Two of these six patients were crossed over to treatment with MECY because of tumor relapse after 10 months of therapy. Three other patients were treated with MECY after second-look surgery revealed residual tumor. One patient received whole-abdominal radiotherapy after second-look surgery revealed minimal residual tumor. In addition, one of these patients had impaired hearing.

One patient treated with CHAD had abnormally low left ventricular ejection fractions on two of five occasions for which the doxorubicin was withheld.

There were no chemotherapy-related deaths in this study.

Laparoscopic Evaluation

Table 4 shows the laparoscopic findings in an attempt to study correlations between the findings at interim laparoscopy and subsequent course of the disease. Of the patients in each chemotherapeutic arm, there were 12 and 13, respectively, who were evaluable by interim laparoscopy. The five nonevaluable patients in the DDP-MECY group were three patients who had clinically evident tumor progression, one patient with poor visualization, and one patient in whom interim laparoscopy was not attempted because of known dense intra-abdominal adhesions. The three nonevaluable patients in the DDP-CHAD group were two patients with unsatisfactory visualization and one patient who was lost to follow-up.

Approximately one-half of the interim laparoscopies after 6 months of therapy were negative: seven of 12 and six of 13 of the DDP-MECY and DDP-CHAD patient groups, respectively. Despite similar numbers of negative interim laparoscopies, only one of six of the DDP-CHAD patients went on to have a negative second-look laparotomy at the end of 1 year of therapy. This compares with seven of seven negative second-look laparotomies after a negative interim laparoscopy in the DDP-MECY patients. This clearly indicates a high degree of relapse, rather than a failure to respond, with the DDP-CHAD regimen. No patient treated with DDP-MECY who had a negative interim laparoscopy after 6 months was found to have relapsed at the time of the second-look after 1 year of therapy. However, five of six of the patients treated with DDP-CHAD with negative interim laparoscopies had positive second-look procedures.

Five of 12 and seven of 13 of the interim laparoscopies were positive for the two groups, respectively. It is of interest that of the five positive interim laparoscopies in the DDP-MECY group, four of the five were positive only by virtue of the fact that there was positive cytology. There was no macroscopic tumor and negative biopsies.

TABLE 4.—Correlations between interim evaluation laparoscopy and subsequent course of disease*

	Treatment group		
	DDP-MECY	DDP-CHAD	Total
Total	17	16	33
Evaluated by interim laparoscopy	12	13	25
Negative interim laparoscopy	7	6	13
Negative interim laparoscopies and negative second-look procedures	7	1	8
Negative interim laparoscopy and positive second-look procedures	0	5	5
Positive interim laparoscopy	5	7	12
Positive interim laparoscopy and positive second-look procedures	4	7	11
Positive interim laparoscopy and negative second-look procedures	1	0	1

* Values = No. of patients.

On the other hand, only two of seven positive interim laparoscopies in the DDP-CHAD group were positive because of positive cytology *only*. The remainder had visualizable tumor nodules and had positive biopsies as well as a positive cytology.

In the DDP-MECY treatment group one patient, who had a positive interim laparoscopy because of positive cytology only, had a negative second-look laparotomy at the end of 1 year. Four of the five patients in the DDP-MECY group with positive interim laparoscopies had positive second-looks. All seven of the patients who had positive interim laparoscopies treated with DDP-CHAD had subsequent positive second-look procedures at the end of 1 year.

DISCUSSION AND CONCLUSIONS

Because the tumor reductive surgery has become more aggressive, and because the newer drug combination regimens are more effective, fewer patients with advanced-stage ovarian carcinoma have measurable clinical parameters to follow during chemotherapy. Most of the patients in the present study had no clinically measurable disease at the end of 2 or 3 months of therapy. Interim laparoscopy was a well-tolerated and sensitive method of evaluation. The laparoscopic criteria used in this study to differentiate between complete and partial responses are rigorous and revealing. In particular, positive cytology on washings obtained at the time of laparoscopy seemed to reflect accurately the status of the disease. There was only one patient with positive cytologic washings at the 6-month interim laparoscopy who was subsequently found to be free of disease at the time of second-look. After further study, it may become apparent that all patients who show less than a complete response by strict laparoscopic criteria after 6 months of therapy should be treated by an alternate therapeutic regimen. The challenge is to strive for high percentages of laparotomy-documented complete remission (negative second-look), which is the most critical correlate of long-term survival and cure and consequently a very meaningful prognostic parameter. To achieve this requires effective drug regimens with low relapse rates. Also, parenthetically, it is important to use one's most effective chemotherapeutic regimen as initial therapy in this disease. It is indeed rare to have a negative second-look after one has failed primary therapy.

The alternating chemotherapeutic regimen of DDP-MECY detailed in this report has been remarkably successful. Four weekly doses of DDP had previously been shown to induce objective, clinically measurable responses in 83% of patients (33% complete responses) (9). The multidrug regimen MECY has been shown to be a synergistic combination of high-dose methotrexate and cyclophosphamide (10), with a high level of activity against epithelial ovarian cancers (7) (67% responders by clinical criteria with 48% complete responders). The results with the alternating regimen DDP-MECY in the present study are significantly better than with MECY alone in an earlier trial. In an earlier MECY study (7), seven of 23 patients (30%) were eligible for second-look procedures; of these, only two of 23 (9%) had negative second-looks.[4] This compares with a second-look eligibility rate of 65% (11 of 17 patients) and a negative second-look rate of 47% (eight of 17) in the present study with the DDP-MECY regimen. These high negative second-look rates are truly exciting. The DDP-MECY program proved to be statistically significantly superior to DDP-CHAD. Although the laparoscopically documented response rates at 6 months were similar, the statistically significantly higher relapse rate and lower rate of negative second-look procedures with DDP-CHAD argue

[4] Barlow JJ. Unpublished data.

strongly in favor of the DDP-MECY regimen. For improved convenience, a shortened 3-day MECY regimen is being tested.

The DDP-MECY combination was better tolerated with respect to toxicity than was DDP-CHAD, which produced moderate to severe neurotoxicity in some of the patients.

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Therapy for Multiple Myeloma With Alternating Non-Cross-Resistant Chemotherapy Combinations: Heterogeneity of Tumor Responsiveness[1,2]

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Thirty-five previously untreated patients with multiple myeloma were treated with a 60-week course of alternating, potentially non-cross-resistant chemotherapy combinations (melphalan and prednisone; vincristine, cyclophosphamide, doxorubicin, and prednisone; and carmustine, melphalan, and prednisone), alternating every 15 weeks in an attempt to prevent the development of drug resistance. The overall objective response rate (> 50% decrease in M protein) was 60% and six patients (17%) had a complete disappearance of the M protein. After 60 weeks, chemotherapy was discontinued in 17 responding or stable patients until relapse occurred from 4 to 39 months later (median, 12 months). Patients relapsing late (> 12 months after discontinuation of therapy) responded more frequently than those relapsing earlier to the reinstitution of the same chemotherapy program. The overall response rate and the actuarial median survival of 26 months in the 35 patients do not differ from the results reported recently with nonalternating combinations given until clinical tumor progression. The failure of this study to prolong survival by using alternating regimens may be due to (*a*) the likely possibility that the initial two regimens are not actually non-cross-resistant in most myeloma patients, and (*b*) the long interval between the alternating regimens, particularly in the face of the low response rate to the initial regimen of melphalan and prednisone. [Cancer Treat Rep 68:1439–1446, 1984]

Drug-resistant clones of malignant cells have long been postulated to be a major reason for the failure of chemotherapy. Recently, it has been suggested that there is a high probability that such drug-resistant tumor clones are present when there is a high tumor burden (1). This has led to the suggestion that the early utilization of alternating combinations of non-cross-resistant chemotherapy might increase the killing of these drug-resistant clones of tumor cells and thus improve the therapy of various malignancies (1,2).

Several drugs are potentially non-cross-resistant in the treatment of multiple myeloma. The introduction of alkylating agents led to an improvement in median survival of at least 1 year in patients with multiple myeloma (3). Subsequent studies showed that other types of drugs were active, including nitrosoureas (4), anthracyclines (5,6), and vinca alkaloids (7,8). In some studies these drugs appeared to be active when the myeloma had progressed during therapy with one of the other classes of drugs. Even when disease progression occurred during therapy with one alkylating drug (eg, melphalan), an objective response to a second, different alkylating drug (cyclophosphamide) (9) was noted in some patients, although the response rate appears to be less than that earlier reported (10). A natural first step was to combine these various drugs. Although combination chemotherapy led to dramatic improvement in complete response rates and survival in some tumors, the use of multiple drugs made only a small improvement over therapy with melphalan alone or in combination with prednisone in patients with multiple myeloma (11,12). In these studies, new single agents or drug combinations were only given at the time of tumor progression. Even with combination chemotherapy, the reported median survival in most series is < 32 months (12,13) and few if any patients are cured.

The approach used in the phase II study reported here was to determine if treatment of multiple myeloma with

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alternating chemotherapy of potentially non-cross-resistant combinations would result in increased killing of tumor cells and thus increased survival without undue toxicity. Such a study requires that the response of patients be monitored in detail to determine if non-cross-resistant combinations are indeed effective.

MATERIALS AND METHODS

Patient Characteristics

Thirty-five consecutive previously untreated patients presenting with multiple myeloma were treated. The clinical characteristics of the patients are shown in table 1. All of the patients had histologically confirmed multiple myeloma with > 20% atypical plasma cells in the bone marrow aspirate or biopsy. One patient with an IgM paraprotein was included because his marrow infiltrate showed typical plasma cells (not plasmacytoid lymphocytes), and his clinical features including the presence of lytic bone lesions were most consistent with plasma cell myeloma. The patients were staged according to the system of Durie and Salmon (14). Using this classification, 25 of 35 patients had a high tumor burden and/or abnormal renal function (stages IIB, IIIA, and IIIB). Eleven of 35 patients had severely diminished performance capacity as defined by the Eastern Cooperative Oncology Group (ECOG) performance criteria (ECOG performance score of 3 or 4). The myeloma protein type is shown in table 1. Three patients had nonsecretory myeloma. All three patients had lytic bone lesions and typical myeloma cell infiltrates in the marrow. One patient with nonsecretory myeloma had plasma cell leukemia, with 50% of the peripheral blood plasma cells containing intracytoplasmic μ chains. Intracytoplasmic kappa chains were detected in the myeloma cells of the second patient, and no immunoglobulin was found in the cells of the third.

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Total	35
Median age in yrs (range): 59 (30-78)	
White/black	23/12
Male/female	23/12
M-protein type	
IgGκ*	13
IgGλ	5
IgAκ	5
IgAλ	4
IgMκ	1
κ light chain	2
λ light chain	1
Nonsecretory	3
Stage	
IA	5
IIA	5
IIB	2
IIIA	17
IIIB	6
ECOG performance status	
1	18
2	6
3	4
4	7

* Light chain of 1 IgG was not typed.

Treatment Protocol

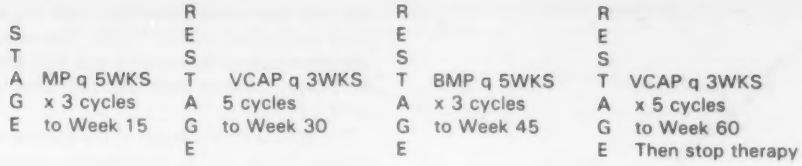
The treatment scheme is outlined in figure 1. Melphalan (10 mg/m^2 orally each day for 4 days) and prednisone (60 mg/m^2 orally each day for 4 days) (MP) was repeated every 5 weeks for three cycles (15 weeks of therapy) unless the patient progressed during the first cycle as demonstrated by an increasing M protein, development or worsening of hypercalcemia, or deterioration in renal function. Subsequently, five cycles of 3 weeks' duration consisting of vincristine (1.4 mg/m^2 [maximum dose, 2.0 mg]), cyclophosphamide (500 mg/m^2), and doxorubicin (45 mg/m^2), all given iv on the first day of each cycle, and prednisone (60 mg/m^2 given orally each day for the first 4 days of each cycle) were given (VCAP).

This was followed by carmustine (BCNU) (100 mg/m^2 iv on Day 1), melphalan (8 mg/m^2 orally each day for 4 days), and prednisone (60 mg/m^2 each day for 4 days) (BMP). This combination was repeated every 5 weeks for three cycles.

After MP, VCAP, and BMP patients again received VCAP for five cycles of 3 weeks' duration. At this time (approximately 60 weeks after the initiation of therapy) patients with stable M-protein levels had their therapy discontinued. Therapy was discontinued and patients had follow-up with an M-protein determination every 4-5 weeks and a marrow aspirate and biopsy every 15 weeks, until progressive disease developed as documented by a 50% rise in the myeloma protein, the development of lytic bone lesions, hypercalcemia, deterioration in renal function, or a fall in the hemoglobin. The treatment protocol was then resumed as described above. Doses of drugs were modified according to protocol guidelines for hematologic, renal, cardiac, or neurological toxicity. Doxorubicin and vincristine doses were modified for hepatic dysfunction (ie, a 50% reduction in dose if the bilirubin was > 1.5 mg/100 ml and a 75% reduction in dose if the bilirubin was > 3.0 mg/100 ml). When patients had received a total doxorubicin dose of 500 mg/m^2 it was discontinued and VCP was given (with a higher dose of cyclophosphamide, ie, 750 mg/m^2).

Criteria for Assessing Response and Disease Progression

The criteria for response were similar to those of the Chronic Leukemia-Myeloma Task Force (15) and were re-



MP =	Melphalan	10 mg/M²	po qdX4
	Prednisone	60 mg/M²	po qdX4
VCAP =	Vincristine	1.4 mg/M²	IV day 1 (max 2.0 mg)
	Cyclophosphamide	500 mg/M²	IV day 1
	Adriamycin	45 mg/M²	IV day 1
	Prednisone	60 mg/M²	po qdX4
BMP =	BCNU	100 mg/M²	IV day 1
	Melphalan	8 mg/M²	po qdX4
	Prednisone	60 mg/M²	po qdX4

FIGURE 1.—Scheme for the myeloma treatment program used in this study.

applied to each patient at the end of each new potentially non-cross-resistant treatment. Complete response was defined as the disappearance of serum and urine M protein and definite evidence of skeletal healing. Partial response was defined as a 50% fall in M-protein level on two consecutive determinations. No change was defined as a < 50% increase or decrease in serum or urinary protein levels, a < 50% increase or decrease in the size of measurable plasmacytomas, and no new areas of malignant disease.

To independently assess the pattern of response to each combination, a 25% fall in paraprotein level was considered significant during the 15 weeks of each combination.

Disease progression was defined by any one of the following: (*a*) a > 50% increase in serum or urinary protein levels over its nadir (minimum change at least 1 g/100 ml if myeloma protein < 1 g/100 ml at nadir), with the increase noted in two consecutive determinations separated by at least 2 weeks; (*b*) a > 50% increase in the product of the two largest diameters of a clearly measurable lesion, or the appearance of new areas of malignant disease; and (*c*) an increase in marrow plasma cells by 50% accompanied by a fall in hemoglobin of 2 g/100 ml below the maximum obtained or the development of hypercalcemia or azotemia.

Statistical Methods

Statistical comparisons of various subgroups were done using Fisher's exact test. Survival analyses were done by life-table analysis, and groups were compared by log-rank analysis (16). All statistical results are two-sided.

RESULTS

Response and Survival

Twenty-one patients (60%) had an objective response, including six patients (17%) who had a complete response. The actuarial survival of all patients entered in the study is shown in figure 2A. The actuarial median survival was 26 months, with an average follow-up period of 31 months; 14 patients are still alive. Seventeen percent of the patients died in the first 10 months. The projected 5-year actuarial survival rate was 22%.

The pattern of response (≥ 25% fall in M protein) to the various cycles was evaluated in 28 patients. Four different patterns were identified (table 2; fig 3). In eight patients (Group A) there was a > 25% fall in the M protein in response to MP, but a < 25% fall in response to VCAP. The overall response (> 50% fall in M protein) in this group was six of eight patients. In nine patients (Group B) at least a 25% reduction occurred following MP with a further reduction of at least 25% after VCAP. Following BMP there was a further fall detected in one patient. All nine patients responded, with five complete responses (disappearance of the M protein on electrophoresis). Nine patients (Group C) showed a < 25% decrease to MP but a > 25% response after VCAP. Three of these nine patients had a ≥ 50% fall in M protein after 60 weeks of therapy. Of these nine patients, one (No. 19) showed progression during BMP and subsequently responded to VCAP, suggesting that the patient's tumor was resistant to MP. One patient in Group C (No. 20) showed a 70% reduction in M protein following BMP, suggesting that the tumor was responsive to BCNU since it had not initially responded

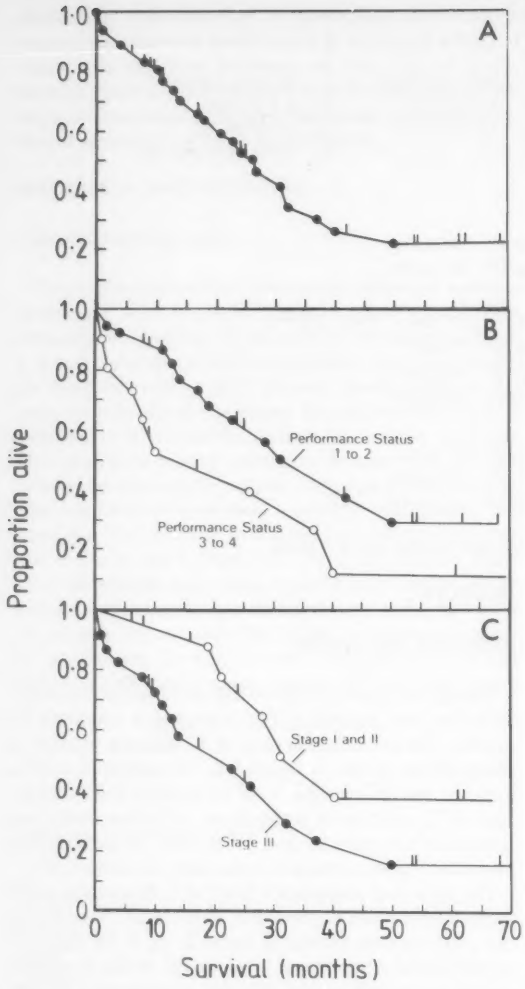


FIGURE 2.—A. Actuarial survival of all patients. B. Actuarial survival of patients with ECOG performance status of 0-2 and 3-4. C. Effect of disease stage on actuarial survival. 1 patient was not assigned a stage and is not shown.

to MP. Group D (not shown) contained two patients who did not respond to any combination. The pattern of response could not be evaluated in seven patients because they had nonsecretory myeloma or died too early. There was no significant difference in actuarial survival among groups A, B, and C.

The therapy during which a response (50% fall in M protein) first occurred was evenly distributed between the MP (or BMP) and VCAP combinations. Ten patients had a response to MP within the first 15 weeks. There were six new responders after the first cycle of VCAP, one new responder after BMP, and two new responders after the second cycle of VCAP. The mean fall in M protein after each of these cycles was 33% after MP, 18% after VCAP, 5% after BMP, and 13% after the second cycle of VCAP.

The effects of the stage of the disease at presentation and the initial ECOG performance status are shown in figure 2, B and C. Low-stage patients and good performance status patients lived longer than patients with advanced stage ($P = 0.1$) and poor performance status ($P = 0.1$). These differences, however, did not reach significance given the small patient numbers.

Effect of Restarting Chemotherapy After an Unmaintained Period

Twenty-one patients have been in the study > 15 months; nine died prior to 15 months and five have been in the study for < 15 months. Therapy was stopped after 15 months in all 14 responders and in three of seven nonresponders who were asymptomatic (table 3). Of the 14 responders, one died in remission, one is still in remission, and 12 have relapsed. The chemotherapy combinations were reinstituted in these 12 patients who relapsed. After reinstitution of therapy, five of 12 patients responded again (table 3), including one of six who relapsed prior to 12 months and four of six who relapsed after 12 months. The median survival from diagnosis of the early relapsing patients was 32 months (range, 23-42+), whereas it has not been reached for the late relapsing patients (> 52 months). Neither stage, pattern of response, nor the magnitude of the initial response was useful in predicting early or late relapses. Interestingly, the three asymptomatic patients who had not achieved a > 50% decrease in M protein (Nos. 22, 31, and 34) have remained off treatment for 61+, 62+, and 25+ months, respectively.

Discrepancy Between Change in M-Protein Level and the Patient's Condition

In three patients clinical evidence of relapse was not accompanied by a rise in the paraprotein level. In one patient (No. 7), the M-protein level fell, although the patient developed plasma cell leukemia. The second patient (No. 15) relapsed with an increasing M protein, achieved a response, and then relapsed again without a rise in the M protein. In the third patient (No. 14), the disease pro-

TABLE 2.—Patterns of change in M-protein levels

Pattern	MP*	VCAP*	No. of patients
A	⩾ 25%	< 25%	8
B	⩾ 25%	⩾ 25%	9
C	< 25%	⩾ 25%	9
D	< 25%	< 25%	2

* % decrease in M-protein level during the 1st course of MP or VCAP.

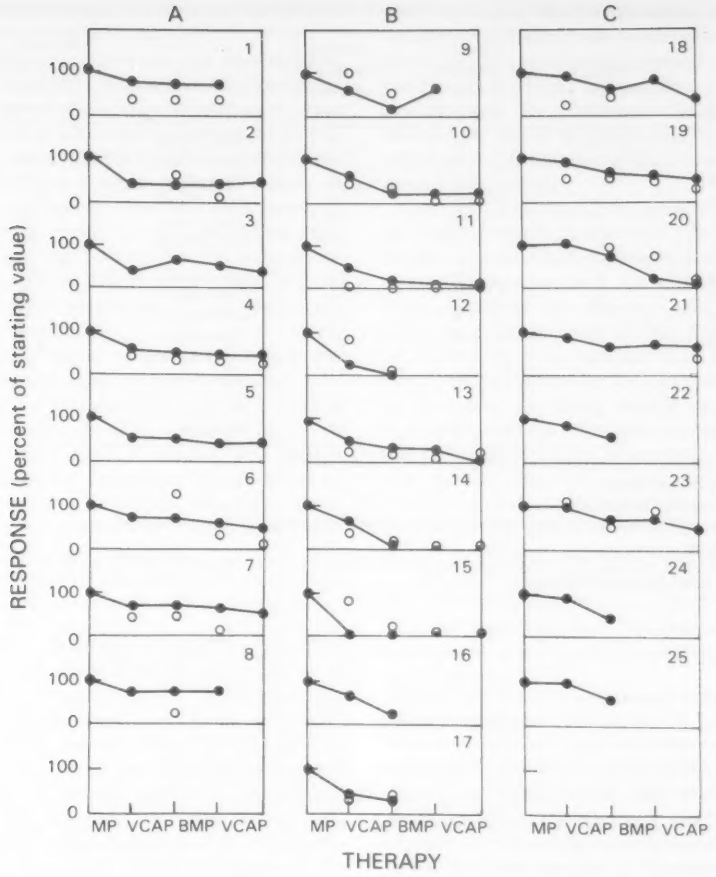


FIGURE 3.—Patients were grouped by pattern of response into 3 columns labeled A, B, and C. M-protein levels are shown in closed circles and % of plasma cells in the marrow by open circles. The M-protein level and the % of plasma cells in the marrow are expressed as a % of the starting value. Therapy is indicated as MP, VCAP, or BMP (*see* fig 1). Serum M-protein levels are shown for each patient except Nos. 15 and 20, who only had Bence Jones proteinuria and for whom urinary M-protein levels are shown.

gressed without a concomitant rise in the M protein. Serial measurements of M protein and bone marrow plasma cell percentages correlated poorly with one another (correlation coefficient, 0.2).

Toxicity

Table 4 shows the nadir counts recorded for each of the induction treatment combinations. Severe neutropenia and thrombocytopenia were not a serious problem in most patients during the first 60 weeks (four cycles) of therapy. Episodes of infection were documented in 39% of the patients. The infections included gram-negative urinary infections (five patients); pneumonia due to pneumococcus (two) and mixed organisms (one); pulmonary aspergillosis (one); cryptococcal meningitis (one); cellulitis (two); and fever with no micro-organism cultured (five).

Two patients died unexpectedly in partial remission of causes not related to their treatment or their disease, one at 13 months and the other at 17 months. Another patient had a myocardial infarct and died in cardiac failure. The patient had received only 90 mg of doxorubicin. No deaths were clearly therapy-related. One other patient developed congestive cardiac failure after a total doxorubicin dose of 375 mg/m^2. No patient developed myeloid leukemia.

TABLE 3.—Relationship between pattern of response, duration of unmaintained remission, time to relapse, and response to reinduction in 14 patients

Patient No.	Stage	Pattern of response*	Response to induction† (% fall in M protein)	Duration of unmaintained remission (mos)	Outcome	Response to reinduction‡ (% fall in M protein)	Survival from initial treatment (mos)
7	IIIA	A	50	4	Early relapse	§	23
3	IIIA	A	60	4	Early relapse	29	32
13	IIB	B	100	6	Early relapse	67	28
14	IIIB	B	100	8	Early relapse	¶	37
19	IIA	C	50	9	Early relapse	39	40
4	IA	A	54	12	Early relapse	40	42+
20	IIIB	C	100	13	Late relapse	100	50
6	IIIA	A	50	14	Late relapse	35	32
15	IIIA	B	100	14	Late relapse	100	54+
11	IIIA	B	100	15	Late relapse	100	54+
18	IA	C	60	16	Late relapse	**	31
5	IIIA	A	60	39	Late relapse	53	68+
21	IA	C	62	9+	No relapse	—	24+
10††	IIIB	B	73	3+	No relapse	—	17

*Pattern of response as defined in fig 3. Pattern D is no response to MP, VCAP, or BMP.
†Maximum response to induction therapy.
‡Maximum response to reinduction therapy.
§Paraprotein level fell by 50% but the patient developed plasma cell leukemia with blasts in the peripheral blood.
¶Relapsed without M protein.
**Patient died within 3 wks of receiving MP from pneumonia, pulmonary embolism, and central nervous system involvement with plasma cells.
††This patient died a sudden death while in remission.

DISCUSSION

In this phase II trial we have tested the effectiveness of alternating regimens of potentially non-cross-resistant chemotherapy given before the time of clinically demonstrable tumor progression in patients with multiple myeloma. The results show that patients differ in their response pattern to these chemotherapy regimens. However, we also found no improvement in overall response rate, survival, or survival by response pattern. Thus, while alternating non-cross-resistant chemotherapy was shown to be feasible in this study, it did not appear to offer a major advantage over conventionally designed chemotherapy programs using multiple agents. The overall response rate of 60% and the median survival of 26 months achieved in this study are similar to other recent studies using a single combination chemotherapy regimen continued until progression (12).

The detailed analysis of the responsiveness of the myeloma in individual patients identified marked heterogeneity in responsiveness. The eight patients who responded to MP only and the two patients who did not respond to any of the drugs could not have derived benefit from the alternating therapy. While the nine patients who responded to MP and VCAP may have derived benefit from the alternating therapy, it could be argued that the response to MP was slow and that the M-protein decrease after MP continued during VCAP therapy and was not a response to VCAP. Eight patients had a fall in M protein after VCAP, even though they did not respond to MP. Although it is possible that 15 weeks of therapy did not allow sufficient time to detect a response to MP, it seems more likely that in these patients, the myeloma cells were resistant to MP prior to any therapy being given and that therefore they also could not have derived any benefit from alternating therapy. There were too few patients to do a more detailed analysis of M-protein kinetics and such analyses should be viewed with caution,

TABLE 4.—Hematologic toxicity*

	% of patients with wbc counts (cells/mm^3) of—			% of patients with platelet counts (cells/mm^3) of—	
Therapy	< 500	500-1000	1000-2000	< 50,000	50,000-100,000
MP, Cycle 1	3	0	8	8	13
VCAP, Cycle 1	9	4	26	9	17
BMP, Cycle 1	0	0	11	11	21
VCAP, Cycle 2	0	7	43	11	29

*Nadir counts during each 15-wk cycle of therapy.

since the kinetics of the disappearance of serum and urinary M protein appear to be different (17).

Cyclic therapy for multiple myeloma has been reported in two other studies (18,19). Bergsagel et al (18) reported on the sequential use of three agents (melphalan, cyclophosphamide, and BCNU) each in combination with prednisone compared to the use of the four-drug combination. The sequential treatment yielded equivalent results to the four drugs in combination. The Southwest Oncology Group (SWOG) compared MP to two alternating combinations and reported that both alternating regimens resulted in improved survival (19). It was not clear whether the alternating schedule or the use of more agents resulted in the better survival.

Several other observations were made during the study. The role of maintenance therapy in patients with myeloma has been controversial (20,22,23), but a number of studies have shown it to be of little benefit (24,25). In our study therapy was stopped in patients who were in remission after 60 weeks of treatment. These remissions were maintained from 4 to 39 months. This study therefore confirms that long unmaintained remissions are possible in myeloma after initial treatment.

It was previously reported that 50%–80% of patients with myeloma who relapse after an unmaintained remission (induced by MP) responded to the same chemotherapy used to achieve the initial remission (20,21), and in one study (21) it was noted that a response was more common in late (six of eight patients) than in early (four of 12) relapsing patients. Our findings confirm both these observations. Five of 12 evaluable patients responded to reinduction and second responses (even complete responses) were more frequent in late (four of six patients) than in early relapsing patients (one of six). This finding is similar to that of Fisher et al (26) in relapsing patients with advanced Hodgkin's disease. In contrast to the SWOG studies (20,21), neither the initial stage nor the pattern of response appeared to predict which patients would relapse early, perhaps due to the small numbers in our study.

During careful monitoring of the responses of patients to chemotherapy it was found that although the drop of M protein was a useful marker of disease response and progression in most patients, in three patients with initially secretory myeloma disease progression was not accompanied by an increase in M protein. In one patient, progression was accompanied by the development of plasma cell leukemia. The occurrence of a fulminant relapse not accompanied by a rise in the M protein was also recently reported by Suchman et al (27). This pattern of relapse may be due to the failure of myeloma cells to secrete immunoglobulin at a constant rate, despite previous reports to the contrary (28). Alternatively, it is possible that new clones of nonsecretory cells may arise in some patients. There appears to be reason, then, to monitor myeloma with parameters such as calcium and urea levels as well as M-protein estimations. However, serial estimates of plasma cell levels in the marrow did not prove useful in monitoring disease status and changes in plasma cell levels did not correlate well with M-protein level changes. The explanation for the poor correlation between the fall in M protein and in the level of plasma cells is probably that the infiltration of the marrow with plasma cells is patchy.

The major findings of the present detailed analysis of the responsiveness of myeloma cells to sequential combinations of chemotherapy administered before clinical tumor progression were the marked heterogeneity of drug sensitivity in myeloma cells and the lack of dramatic clinical effect of this approach. Given this heterogeneity, it is possible that the study of individualized chemotherapy for myeloma patients based on in vitro drug sensitivity testing would provide a way around this obstacle (29). Other approaches that might be more successful include the initial use of a more aggressive therapy than MP, more frequent alterations of therapy, or the use of different drugs. While the principle of alternating non-cross-resistant therapies may be sound, truly non-cross-resistant regimens should produce a large number of complete responses in patients who fail the alternative regimen. The results of this and other studies suggest that such non-cross-resistant drug combinations may not be available at the present time in multiple myeloma.

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Effect of Prednisolone on Hormone Profiles During Primary Endocrine Treatment of Advanced Breast Cancer[1]

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Various plasma hormones were measured in 13 pre- and 20 post-menopausal women with advanced breast cancer before and for 12 months after ovarian irradiation or during continuous administration of tamoxifen at a dose of 10 mg twice a day, respectively; some patients received additional prednisolone at a dose of 5 mg twice a day. These patients were taken from a larger clinical trial which demonstrated a higher response to primary endocrine therapy when prednisolone was added. Levels of dehydropiandrosterone sulfate were depressed in patients receiving prednisolone, confirming adrenal suppression. Estradiol levels were reduced in all patients, while luteinizing hormone and follicular stimulating hormone increased after ovarian irradiation, but all three hormones fell during tamoxifen administration; no further changes were caused by the addition of prednisolone. Prolactin and thyroxine remained constant throughout the study. There were no differences between responders and nonresponders in hormone profiles or in changes in the profiles after treatment. [Cancer Treat Rep 68:1447–1453, 1984]

Endocrine therapy may be a useful initial treatment for selected patients with disseminated breast cancer. Ovarian ablation in premenopausal women and the administration of the antiestrogen tamoxifen to postmenopausal women both give a response frequency of about 30% (1,2). Prednisolone is an active agent in this disease and has been shown to produce remissions in 14% of patients > 65 years of age and stabilization of disease for at least 6 months in an additional 21% (3). When given together with ovarian irradiation as part of adjuvant treatment to premenopausal women ⩾ 45 years following mastectomy, prednisolone was associated with a reduced recurrence rate and improved survival when compared with ovarian irradiation alone (4). A preliminary report from this Unit has demonstrated an improved response rate from the addition of prednisolone to ovarian irradiation in premenopausal women and from tamoxifen in postmenopausal women with metastatic or progressive locally advanced breast cancer (5).

The therapeutic mechanism of action of corticoids in advanced breast cancer remains obscure. Prednisolone may act by reducing adrenal steroid hormone synthesis following adrenocorticotropic hormone suppression (6) or by binding to corticosteroid receptors present in breast tumor cells (7). A direct role in cell killing has also been postulated (8). This study attempts to investigate whether the additional clinical benefit obtained when prednisolone is used is due to alterations in endocrine function over and above those induced by primary endocrine treatment, viz ovarian ablation in premenopausal women or by tamoxifen in postmenopausal women.

METHODS

Patients

The patients studied had progressive breast cancer which was confirmed histologically. In addition, their disease was either locally advanced or metastatic and not controllable by local therapy alone. They had not received prior endocrine or other systemic treatment for advanced cancer and were ineligible if they had received systemic corticosteroid therapy in the previous year, if there was a medical contraindication to corticosteroid medication, or

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if there was hypercalcemia not controllable without the use of steroids. Details of the trial are described elsewhere by Stewart et al (5).

Treatment

Thirty-five premenopausal patients were randomized to receive either ovarian irradiation alone (1200 cGy to pelvis) or ovarian irradiation plus prednisolone (5 mg twice a day, starting on the first day of radiotherapy). Two hundred and forty-five postmenopausal patients were randomized to receive either tamoxifen (10 mg twice a day) or tamoxifen plus prednisolone (5 mg twice a day). Treatment was continued until there was evidence of disease progression.

Hormone Analysis

Blood samples from 33 patients in the trial (table 1) were taken at the same time of the day just before and at 1 and 3 months after treatment started, and thereafter at 3-month intervals until disease progression. It was not possible to ensure that the blood samples from the premenopausal patients were collected at the same stage of the menstrual cycle. The blood samples were allowed to clot before centrifugation and the separated sera stored frozen at -20°C. Before analyses, all of the serum samples were aliquoted and number coded to ensure that they were not repeatedly frozen and thawed and that they were assayed "blind" without prior knowledge of patients' treatment or response. In addition, duplicate samples were also included to assess the reproducibility of the assays. Each sample was analyzed for estradiol (9), dehydroepiandrosterone sulfate (DHA-S) (10), and prolactin (11). Follicular stimulating hormone (FSH) and luteinizing hormone (LH) were analyzed by a double antibody radioimmunoassay by Technical Laboratory Services and the thyroid function index (TFI) was assayed using Quanta-Count T4/TF1 ^{125}I-labeled radioimmunoassay kits (Bio-Rad Laboratories Ltd, Watford, United Kingdom).

The precision of the assays was calculated using the formula:

$$\text{standard deviation} = \sqrt{\frac{\Sigma d^2}{2N}},$$

where d is the difference between duplicate serum samples and N is the number of comparisons. The results are shown in table 2.

Statistics

Since the data cannot be assumed to be normally distributed, statistical significance between groups was assessed using the Wilcoxon rank test for paired and unpaired data. However, for convenience, hormone concentrations are described using arithmetic means ± standard errors of the mean.

Assessment of Response Criteria

Before entry in the trial, a full physical examination was performed, measurements were made of all palpable lesions, and all visible lesions were photographed. All patients had chest radiograph, bone scintiscan with radiographs of areas of increased isotope uptake, liver scintiscan, cbc, and biochemical screen. Baseline lesions were selected for serial assessment. Patients were followed at 4-week intervals with repeat assessment of baseline lesions and photographs. Bone scintiscans, chest radiographs, radiographs of skeletal lesions, cbcs, and biochemical screens were repeated at 3-month intervals.

Objective response was assessed by International Union Against Cancer criteria (12). The records of all responders from when the trial started in August 1978 until December 1980 were reviewed by two independent external reviewers; the records of all other patients have been internally reviewed. The categories of response were defined as follows: *complete response (CR)*—the disappearance of all known disease; *partial response (PR)*—a ≥ 50% decrease in the sum of the products of the perpendicular axes of measurable lesions and objective

TABLE 1.—Details of patients studied*

Treatment category	No. of patients	Median age in yrs (range)	Objective response				ER status		
			CR	PR	NC	PD	ER+	ER−	NK
Premenopausal									
Ovarian irradiation	7	44 (30-50)	1	0	1	5	4	0	3
Ovarian irradiation + prednisolone	6		1	4	1	0	3	1	2
Postmenopausal									
Tamoxifen	10	58 (51-79)	0	4	1	5	8	0	2
Tamoxifen + prednisolone	10		1	5	1	3	9	0	1

* Objective clinical responses were classified as complete (CR) or partial (PR), no change (NC), or progressive disease (PD). Estrogen receptor status (ER) was measured to be positive (ER+), negative (ER−), or was unknown (NK).

TABLE 2.—Precision of hormone assays used

Hormone	N*	Mean	SD	Coefficient of variation (%)
Estradiol	19	22.3 pg/ml	2.47	11
DHA-S	19	44.5 g/100 ml	4.86	13
LH	19	43.0 IU/ml	6.07	14
FSH	18	48.6 IU/ml	5.49	11
Prolactin	16	6.4 ng/ml	1.46	23
TFI	25	2.08 units	0.178	9

*N = No. of comparisons of serum samples.

improvement in evaluable, but nonmeasurable lesions, with no new lesions; *no change*—lesions unchanged, ie, a < 50% decrease or a < 25% increase in the size of measurable lesions; and *progressive disease*—progression of some or all lesions or the appearance of new lesions. Patients recognized as responders had achieved complete or partial response, while nonresponders had stable disease or disease progression.

Estrogen Receptors

For many of the patients, the estrogen receptor (ER) content of their primary or metastatic tumors was estimated by the method of King et al (13). A value of ⩾ 5 fmols of receptor/mg of cytosol protein was regarded as positive (ER+) and any value of < 5 fmols of receptor/mg of cytosol protein was regarded as negative (ER-).

RESULTS

Clinical Response

A greater proportion of the premenopausal women who received ovarian irradiation and prednisolone responded to treatment than those who received ovarian irradiation alone. Similarly, the addition of prednisolone to tamoxifen in postmenopausal women was associated with a significantly better response rate than among those women receiving tamoxifen alone (26 of 73 patients and nine of 72, respectively; $P < 0.01$) (5). Thirty-three of these patients had serial hormone analyses performed on their sera up to 12 months after treatment began and their characteristics and clinical responses to treatment are shown in table 1.

Hormone Analyses

Dehydroepiandrosterone Sulfate

There was a rapid and sustained reduction in serum concentrations of DHA-S in both pre- and post-menopausal patients receiving prednisolone, but no significant change in concentrations in patients treated with irradiation or tamoxifen alone (fig 1). Basal values of DHA-S varied considerably, but there was no relationship between the absolute basal values and subsequent response to treatment.

Estradiol

Ovarian irradiation reduced serum estradiol to 22% of pretreatment values in premenopausal patients but the addition of prednisolone had no further effect (fig 2). In postmenopausal patients, mean serum levels of estradiol tended to decrease over the 12 months of treatment but these reductions were not statistically significant (reductions from each basal to mean of 3-12-month levels of 7.0 ± 3.8 and 4.6 ± 1.7 pg/ml in tamoxifen-treated patients with and without prednisolone, respectively; $P > 0.05$).

Follicular Stimulating Hormone and Luteinizing Hormone

Pituitary gonadotropin levels rose after ovarian irradiation, reaching a plateau at 3 months, but this effect was not further altered by the addition of prednisolone as shown in figures 3 and 4. Tamoxifen caused a reduction of approximately 25% in mean levels of the gonadotropins, regardless of the addition of prednisolone (figs 3 and 4).

Prolactin

Serum levels of prolactin remained constant, being unaffected by any of the treatment regimens (table 3). Basal levels were slightly higher in the younger patients, but this difference was not significant.

Thyroid Function Index

Serum levels of "free thyroxine" as measured by the TFI remained constant throughout the study and were not altered by prednisolone (table 3). One patient was found to be hypothyroid and required replacement thyroxine medication; serum levels from this patient were excluded from analysis.

Correlations Between Hormone Levels and Clinical Response

When patients were divided into responders and nonre-

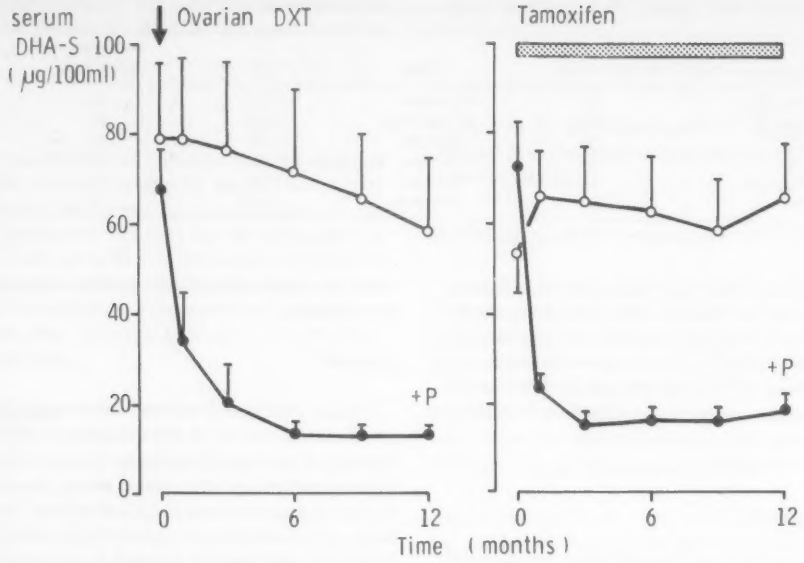

FIGURE 1.—Effect of ovarian irradiation (DXT) and tamoxifen on serum levels of DHA-S in pre- and post-menopausal patients, respectively, during the 12 mos after treatment started. Closed circles represent levels in patients treated additionally with prednisolone (P).

sponders to treatment, there was no statistically significant difference observed in any of the hormone profiles, except for DHA-S levels in the premenopausal patients. In this group, those who responded to treatment had a lower median level after 3 months than those who did not respond (12 and 60 μg/100 ml, respectively; $P < 0.03$). This is of doubtful meaning because of the small numbers of these premenopausal patients and their uneven matching with respect to objective response achieved (of seven patients treated by ovarian irradiation alone, five did not respond, whereas five of six given irradiation and prednisolone responded to their treatment). In postmeno-

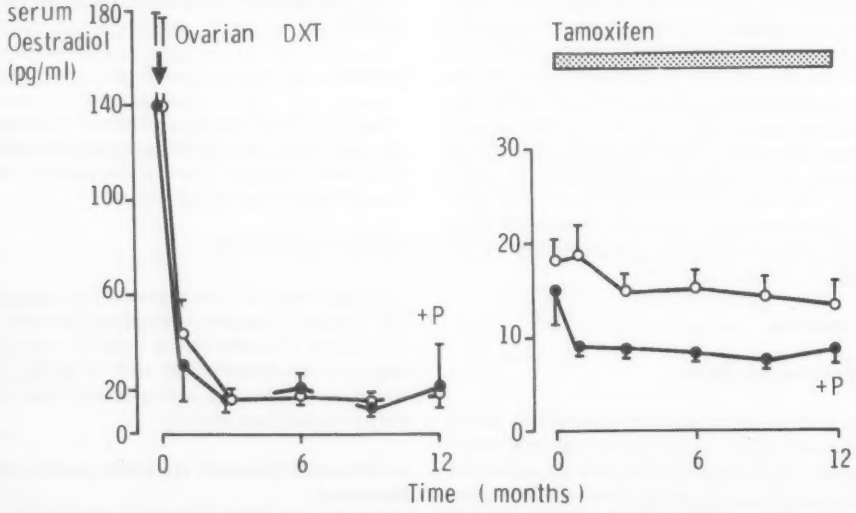

FIGURE 2.—Effect of ovarian irradiation (DXT) and tamoxifen on serum levels of estradiol in pre- and post-menopausal patients, respectively, during the 12 mos after treatment started. Closed circles represent levels in patients treated additionally with prednisolone (P).

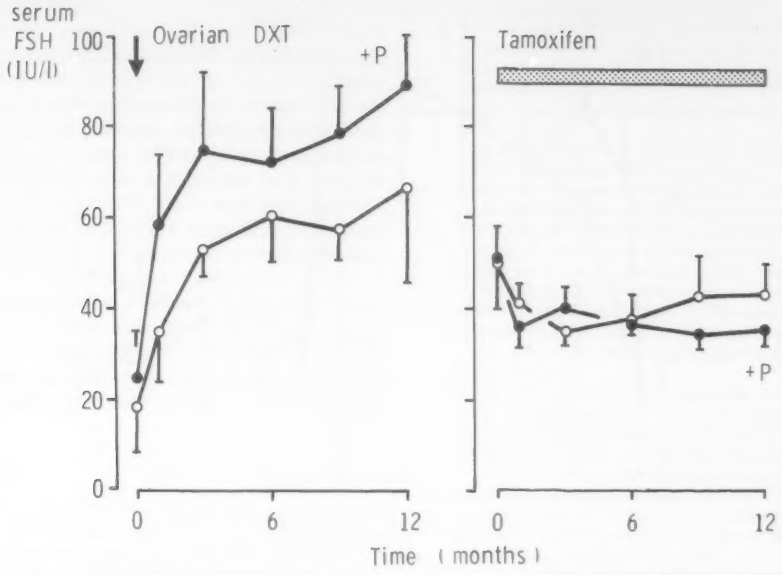

FIGURE 3.—Effect of ovarian irradiation (DXT) and tamoxifen on serum levels of FSH in pre- and post-menopausal patients, respectively, during the 12 mos after treatment started. Closed circles represent levels in patients treated additionally with prednisolone (P).

pausal women serum estradiol levels tended to be lower in those who responded and reflected the greater proportion being treated with prednisolone; however, these levels were not significantly different from those in women who failed to respond.

DISCUSSION

The results of the study indicating that corticosteroids used in conjunction with other endocrine therapies are associated with an increase in response rate in patients with advanced disease (5) may be partially explained on endocrine grounds. Theoretically, the therapeutic action of prednisolone may be via its suppression of adrenal hormone synthesis following adrenocorticotropic hormone suppression (6) or by binding to corticosteroid receptors present in breast cells (7). Thus, prednisolone considerably depresses adrenal function (as measured by DHA-S secretion) in premenopausal patients treated by ovarian irradiation and in postmenopausal women treated with tamoxifen, ie, a partial "medical adrenalectomy" is achieved. What is surprising, however, is the lack of effect on serum estradiol and hence prolactin in premenopausal women, especially in the presence of an increase in FSH levels in the prednisolone-treated group. If, in oophorectomized or postmenopausal women, the main source of estrogens is derived from the peripheral conversion of adrenal androgens (14), then a pronounced fall in blood estrogen levels should have been expected, as has been found for urinary estrogens (15). It may be that measurement of total serum estradiol is inappropriate, since recent work has shown that estradiol not bound to

TABLE 3.—Serum concentrations of prolactin and TFI before and during 12 mos after primary endocrine treatment was started

	Time (mos)							
	0	1	6	12	0	1	6	12
Premenopausal								
	Ovarian irradiation (n = 7)				*Ovarian irradiation + prednisolone (n = 6)*			
Prolactin (ng/ml)	11 ± 4	6.8 ± 2	11 ± 4	15 ± 6	15 ± 6	17 ± 8	11 ± 4	11 ± 5
TFI (units)	2.1 ± 0.2	2.0 ± 0.03	2.4 ± 0.3	2.2 ± 0.4	2.0 ± 0.4	2.0 ± 0.2	2.3 ± 0.1	2.1 ± 0.2
Postmenopausal								
	Tamoxifen (n = 10)				*Tamoxifen + prednisolone (n = 10)*			
Prolactin (ng/ml)	8.2 ± 3	6.2 ± 1	11 ± 6	11 ± 3	8.7 ± 2	6.5 ± 2	7.2 ± 2	8.4 ± 3
TFI (units)	1.9 ± 0.2	2.0 ± 0.2	2.1 ± 0.2	2.2 ± 0.2	2.0 ± 0.2	2.1 ± 0.1	2.0 ± 0.1	2.2 ± 0.2

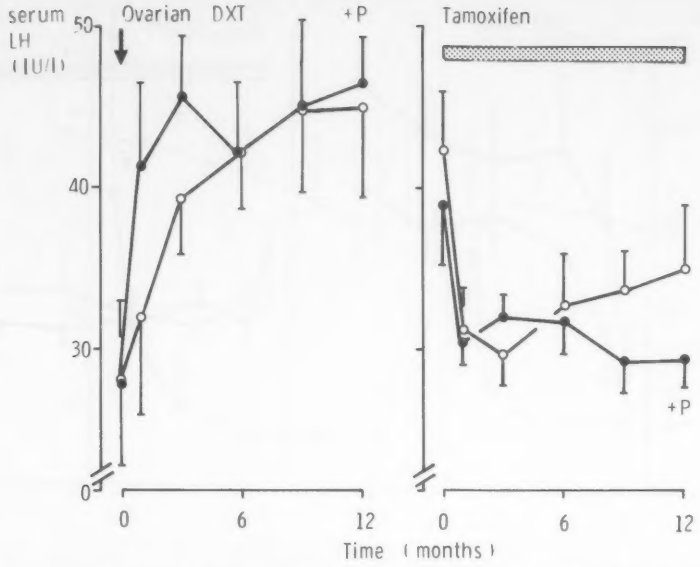

FIGURE 4.—Effect of ovarian irradiation (DXT) and tamoxifen on serum levels of LH in pre- and post-menopausal patients, respectively, during the 12 mos after treatment started. Closed circles represent levels in patients treated additionally with prednisolone (P).

serum proteins (especially sex hormone binding globulin) is the biologically active fraction (16). It is also of interest that free estradiol is raised in women with breast cancer.

The results in this paper do little to clear up the uncertainties concerning the effects of tamoxifen on endocrine function. Tamoxifen is known to bind competitively to estrogen receptors in the target tissue, and its efficacy may be due to the consequent estrogen antagonist activity (17) or even its partial agonist action (18). It has been reported that the drug does not affect blood estradiol levels (19–21) or cause an increase in patients who respond to tamoxifen treatment (22). We failed to find a significant reduction in serum estradiol levels in postmenopausal patients treated with tamoxifen, although mean levels fell; however, levels in the younger women treated with ovarian irradiation fell significantly. Serum levels of the gonadotropins were reduced by tamoxifen and these results are consistent with other studies (19,22–24). However, unlike Golder et al (19), who describe a biphasic response of FSH in responders after 3 months of treatment with tamoxifen, this study found no difference in serum concentrations of responders and nonresponders, even after 12 months of treatment. The small number of premenopausal women treated with prednisolone had higher mean levels of FSH than those receiving ovarian irradiation alone, although the difference failed to reach statistical significance. It would be interesting to measure the serum gonadotropin levels from a larger number of premenopausal patients. Serum levels of prolactin were unchanged, in agreement with previous findings (19,23), although Helgason et al (24) reported a rise in levels. The absence of any demonstrable change in serum levels of "free thyroxine" by primary endocrine therapy with or without prednisolone has not previously been reported. These findings, however, do not support studies reported by Nicolaff et al (25), which postulate a role for glucocorticoids in regulating thyroid activity in man.

No obvious endocrine event was correlated with objective clinical response. Overall, endocrine therapy is particularly effective in patients with estrogen receptors in their original tumors. The small subgroup of patients from this trial who had hormone analyses performed were reasonably well-matched with respect to estrogen receptor status. However, the premenopausal patients were poorly matched for objective response achieved (table 1). There is a suggestion that a reduction in the circulating levels of DHA-S are associated with a favorable clinical response; the absence of such a reduction does not preclude the possibility of such a response. If hormonal mechanisms are postulated as being responsible for tumor regression, it is surprising in this study that it occurs in the presence of appreciable levels of estradiol and prolactin, both hormones which are putative factors in tumor growth. A possible solution to this paradox is that changes in hormone levels are more important in achieving tumor regression than the attainment of low concentrations, thus possibly altering the balance of cell divi-

sion and cell death (26).

Prednisolone has been beneficial in conjunction with ovarian irradiation in the treatment of patients with early breast cancer (4), and a preliminary report indicates a similar effect in the management of women with advanced disease (5). Surprisingly, the response rates were low in this study (5) and a 36% response frequency to tamoxifen and prednisolone was similar to a previous report of tamoxifen alone (27). These results could not be accounted for by any disparity in other prognostic variables; a similar study is in progress to determine whether these results can be confirmed. Prednisolone causes a marked reduction in levels of serum DHA-S in pre- and post-menopausal women with advanced breast cancer. Clearly, more extensive studies, in which attention is also given to free estradiol, are required to elucidate the exact mechanism of this important therapeutic action of prednisolone.

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Teniposide: A Review of 12 Years of Experience[1]

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The root of the mandrake (*Podophyllum peltatum*) is the source of podophyllotoxins, which have been used in folk medicine through the ages, in both American and Asian cultures. Research conducted at Sandoz yielded two derivatives of podophyllotoxin suitable for systemic use: etoposide (VP-16-213) and teniposide (VM-26). Their introduction to the clinic in the early 1970s was almost simultaneous. Their subsequent development has differed greatly. Etoposide has been widely studied alone and in combination in the majority of common tumor types, and is effective in several, notably testicular and small cell lung cancers, lymphoma, leukemia, and Kaposi's sarcoma in patients with the acquired immunodeficiency syndrome (1). Early indications of this activity focused investigator interest on etoposide, with the result that clinical research with teniposide has lagged far behind. We still know relatively little of the true activity of teniposide in most of the major tumors, and even less about its relative merits as compared to etoposide.

However, contrary impressions persist. In the oncology community, there is the perception that teniposide is more active than etoposide in pediatric tumors, and vice versa in adult tumors, and that teniposide is more active than etoposide in acute lymphocytic leukemia (ALL), and vice versa in acute myelocytic leukemia. These perceptions cross geographic boundaries: combination chemotherapy regimens for non-Hodgkin's lymphoma (NHL) in Europe are likely to contain teniposide as the epipodophyllotoxin of choice, while those in the United States contain etoposide. The data which have accrued from clinical trials of the epipodophyllotoxins do not support such perceptions. The somewhat fickle course of their development explains the use of teniposide in a different population of cancer patients. Responses observed in small numbers of patients in early clinical trials led to the evaluation of teniposide in pediatric malignancies, in which the activity of etoposide has been little explored. Adult trials have been conducted predominantly in lymphoma and brain tumors. It is clear from these studies that teniposide is indeed an active antineoplastic drug. The difficulty lies in determining the degree of this activity and, most importantly, its degree relative to that of etoposide.

Here we review the preclinical and clinical data which define the current role of teniposide (fig 1), and indicate the areas in which future studies may establish a place for it in the treatment of cancer.

Mechanism of Action and Cellular Metabolism

Evidence for the mechanism of action of teniposide is derived from studies of both teniposide and etoposide. The epipodophyllotoxins probably exert their cytotoxic effects through interaction with DNA. Unlike the vinca alkaloids and the parent compound podophyllum, etoposide and teniposide do not inhibit microtubule assembly (2,3), nor is there a metabolite produced which does so (4).

Action on DNA

Flow cytometry studies indicate that both compounds delay the transit of cells through S phase (5), followed by arrest in late S or early G_2 (5,6). Treatment of HeLa cells with etoposide (7) or L1210 cells with teniposide (8) induces dose-dependent single-stranded DNA breaks which the cells can repair; inhibition of DNA repair by caffeine or chloroquine markedly enhances cytotoxicity (9). On the other hand, etoposide, unlike alkylating agents, does not induce such damage when incubated with purified DNA in vitro (7). Whether the effect in whole cells requires activation of an endonuclease or is mediated by an intracellular metabolite has not been elucidated. Recent work with the CCRF-CEM line confirms the concentration-dependent scission of DNA, an effect detectable at 0.25 μm, well below the level required for kinetic effects or cytotoxicity (6).

Metabolic activation of etoposide to reactive intermedi-

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ates by rat liver and HeLa cell microsomal fractions has been noted (10), and free radical formation at the pendant phenolic group has been hypothesized (11). Free radical scavengers prevent the formation of single-strand breaks in DNA and inhibit the cytotoxicity of etoposide (11). A mechanism involving inhibition of topoisomerase II has been suggested (12), previously postulated as a common pathway for intercalator-induced DNA scission (13). Thus, while it is clear that the activity of teniposide is mediated through its DNA reactivity, the precise details remain to be elucidated.

Action on Nucleoside Transport

Etoposide and teniposide partially inhibit nucleoside transport in cell lines. This effect involves only the mechanism of facilitated diffusion and occurs only at drug concentrations (30 μm) higher than those required for DNA effects (2,14). The inhibition of incorporation of labeled thymidine into DNA occurs only at low extracellular levels of nucleoside (15). It seems likely, therefore, that nucleoside transport inhibition is not the primary mechanism of action of these drugs. In this connection, however, it is of interest that teniposide and etoposide are synergistic with cytarabine (ara-C) in vitro, and that the combination of teniposide and ara-C has shown marked clinical activity in relapsed ALL in children (16,17). Ongoing studies of nucleotide pools in this setting will further clarify the relationships between nucleoside transport and cytotoxicity.

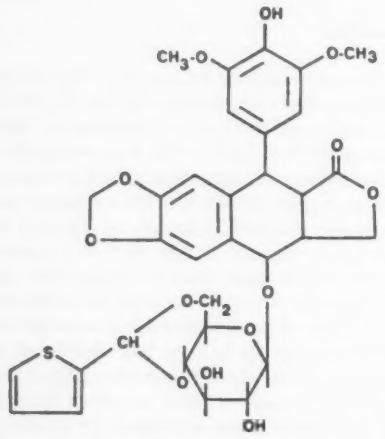

FIGURE 1.—Structure of teniposide. Insoluble in water, it is supplied in 50-mg ampules containing benzyl alcohol, dimethyl acetamide, polyethoxylated castor oil, maleic acid, and absolute alcohol. The final solution is prepared by further diluting each 5-ml ampule in 100 ml of 0.9% sodium chloride or 5% dextrose. While the resulting solution may have a slight opalescence due to the surfactant, it should be discarded if a precipitate is present. This preparation is stable for 4 hrs at room temperature, and should be administered over a period not less than 30 mins.

Mechanisms of Resistance

Resistance to epipodophyllotoxin is associated with diminished intracellular steady-state levels of drug in comparison to the wild-type cell lines (18,19). In Ehrlich ascites cells made resistant to etoposide, enhanced drug extrusion, by a mechanism similar to that mediating anthracycline resistance, is responsible (18); these cells are fully cross-resistant to teniposide (18). In L1210 murine leukemia cells resistant to teniposide, the lowered steady-state levels appear to be a consequence of reduced influx, associated with the appearance of homogenous staining regions, which suggests gene amplification as an underlying mechanism (19). On the other hand, in the human leukemia (CEM) line, the etoposide-resistant variants accumulated the same levels of intracellular etoposide as the sensitive cells, which suggests that more than one mechanism of resistance may exist (20). Teniposide is a potent inducer of genetic mutation and sister chromatid exchange (21) in all lines studied. Cells resistant to teniposide were fully cross-resistant to etoposide, and vice versa (18,20,22). Teniposide-resistant cells are fully (21) or partially (18) cross-resistant to anthracyclines and other intercalators, and while CEM cells resistant to vincristine are cross-resistant to teniposide, CEM cells resistant to teniposide remain sensitive to vincristine (20). Resistance to teniposide is not associated with cross-resistance to cisplatin (18), and the resistant cells may be more sensitive to this agent (22).

The recent rapid growth in our knowledge of the mechanisms by which epipodophyllotoxins exert their cytotoxic effects defines these agents in the class of DNA-reactive drugs. It establishes a background against which may be evaluated the activity of metabolites of teniposide, the biochemical pharmacology of such activity, and, on a broader scale, the relationships of these agents to other drugs of this class. In concert with the further definition of the determinants of resistance, combination chemotherapy regimens with a rationale rooted in basic science may be devised for use in the clinic.

Preclinical Studies

Antitumor Activity

Teniposide is active in several rodent tumors: Sarcoma 180 and Ehrlich ascites are moderately sensitive, and the Walker 256 carcinosarcoma is more markedly sensitive.[4] L1210 leukemia is highly responsive to teniposide, yielding increased life spans of up to 373% (23,24), and many cures. The best results were seen with multiple-dose schedules, especially with drug administration either twice weekly, or every 3 hours on Days 1, 5, and 9.[4] The murine models have also been used to evaluate combina-

[4]Clinical Brochure. VM-26. Bethesda, MD, National Cancer Institute, 1975.

tions involving teniposide. While L1210 leukemia is sensitive to both teniposide and ara-C as single agents, their use in combination doubles survival time and yields several cures (16).

Teniposide and carmustine are synergistic against L1210 in vivo to a degree that varies with the schedule of administration (25). A similar effect has been noted with hexamethylmelamine (26). Potential synergy with methotrexate has been deduced from the observation that teniposide enhances the accumulation of methotrexate and its polyglutamated derivatives in Ehrlich ascites tumor cells in vitro (27).

Pharmacology

Unlike its congener etoposide, teniposide has not been administered orally; hence, no information is available as to its absorption from the gastrointestinal tract.

The distribution and pharmacokinetics of teniposide are summarized in table 1. Creaven and Allen (28,29) administered radiolabeled teniposide to six adults at a dose of 67 mg/m^2, and found a triexponential pattern of plasma decay with a terminal half-life of 21.2 hours. In eight adults with ovarian cancer, using a high-pressure liquid chromatography (HPLC) assay, Sessa et al (30) and D'Incalci et al (31) administered teniposide at 100 mg/m^2 and 150 mg/m^2 iv by 1-hour infusion, and at 150 mg/m^2 by 24-hour infusion; plasma decay was biexponential, with terminal half-lives of 6.9, 6.1, and 9.7 hours, respectively. Also using a HPLC technique in six children treated at 165 mg/m^2, Evans et al (32) found plasma decay to conform to a biexponential model, with a terminal half-life of 9.6 ± 2.7 hours. The volume of distribution in children was found to be consistent with the high degree of protein binding of the drug (> 99%) (33). The prolonged half-life of the radiolabel (with chromatographic extraction) contrasts with the shorter half-life demonstrated by the HPLC method. This discrepancy may be accounted for by (*a*) differing analytical methodologies, (*b*) the number of compartments in the pharmacokinetic model, or (*c*) the small sample sizes in each study. The similarity of pharmacokinetic parameters in the studies of Sessa, D'Incalci, and Evans suggests that the pharmacologic disposition of teniposide is not age-dependent.

Cerebrospinal fluid levels of teniposide have been studied by both radiolabeled drug and HPLC: barely detectable levels have been noted with both techniques (28,30). Examination of drug levels in brain tumor tissue, however, shows significant accumulation in malignant gliomas (34). The highest tumor levels of drug in this study were seen in one patient treated concomitantly with glycerol, an agent which has been used to enhance drug penetration of the blood-brain barrier.

The individual components of systemic clearance of teniposide are not known in detail. In five patients who were administered radiolabeled drug (28), urine recovery of the label was 44.5% ± 8.2% at 72 hours; fecal recovery over this period in four of these patients was 0%-10.1% (mean, 6.4%). Clearance of teniposide in the six pediatric patients reported above (32) was 5.2 ± 1.0 ml/minute/m^2, a value similar to that reported in adults by Sessa et al (30). However, D'Incalci et al (31) found that < 10% of an administered dose was excreted unchanged in the urine.

The major metabolic products appear to be the hydroxy acid, the picro-lactone isomer, and the aglycone. Evans et al (32) separated these metabolites, and by way of in vitro cytokinetic and cytotoxicity studies, showed that only the aglycone retained the anti-DNA activity of the parent compound. D'Incalci et al (31) could not identify the picro-isomer in blood or urine. The persistence of these and other as yet unidentified metabolites is an area of considerable interest. The delineation of the pharmacokinetics of active metabolites should allow the derivation of more appropriate schedules of teniposide administration in the clinic.

Early Clinical Trials

Based on preclinical data suggesting an advantage for intermittent administration, teniposide was evaluated in patients with solid tumors on weekly (35) and daily (36) schedules. The trial by Muggia et al (35) was one of the first phase I trials to begin with a dose derived from toxicology studies in animals, followed by diminishing escalations to a maximum tolerated dose, the method which is universally used today. The dose recommended for phase II trials was 67 mg/m^2 weekly, although it was noted that most patients tolerated 90 mg/m^2 without excessive toxicity. Since then, a variety of phase I-II trials

TABLE 1.—Pharmacokinetics of teniposide

Ref No.	Investigator	Method	No. of patients/dose (mg/m^2)	Model	Terminal half-life (hrs)	Vd_{ss}* (L/m^2)	Clearance (ml/min/m^2)
28, 29	Creaven and Allen	Radiolabel + TLC †	6/67	Triexponential	21.2		
32	Evans et al	HPLC	6/165	Biexponential	9.6	4.4	5.2
30	Sessa et al	HPLC	7/100-150			7-50	8-25

* Vd_{ss} = volume of distribution at steady-state level.
† TLC = thin-layer chromatography.

TABLE 2.—Doses and schedules of teniposide derived from phase I–II studies in adults with solid tumors and children with leukemias

Dose and schedule	No. of evaluable patients	Toxic effect	Investigator (ref No.)
		Adults—solid tumors	
67 mg/m^2 weekly (= MTD*)	24	Leukopenia, hypotension with rapid infusion, nausea	Muggia et al (35)
1 mg/kg/day × 10 2 mg/kg/day × 3	29	Leukopenia, thrombocytopenia, alopecia	Trempe et al (36)
40–80 mg/m^2/day × 5 CI†	13	Myelosuppression	Booser et al (38)
30 mg/m^2/day × 10–20	27	Neutropenia < 2000 cells/mm^3, platelet count < 100,000/mm^3	EORTC (37)
30 mg/m^2/day × 5	158	Gastrointestinal, alopecia	
		Children—leukemias	
165 mg/m^2/day twice weekly	NA‡	Myelosuppression	Rivera et al (17)

*MTD = maximum tolerated dose.
†CI = continuous infusion.
‡NA = not available.

have derived the doses and schedules most commonly used today (table 2).

Myelosuppression has been dose-limiting on all schedules, with moderate alopecia, nausea, and vomiting observed in most patients. In the early trials, the myelosuppression observed was mild, even at the highest doses used. On the weekly schedule, only one of ten patients had a wbc count < 3000/mm^3 (35), while at 30 mg/m^2/day × 10–20 days, the majority of patients had neutrophil counts > 2000/mm^3 (37). Specific data were not provided for the continuous infusion study (38), but a dose of 60 mg/m^2/day × 5 was well-tolerated. It would seem that patients with solid tumors might tolerate doses of teniposide higher than those currently used.

In pediatric patients, a dose of 45 mg/m^2/day for 5 days causes leukopenia in 31% of patients (39); this appears to be a reasonable phase II dose at this schedule in children. In childhood leukemias, Rivera et al (17) have explored maximally tolerated doses of teniposide administered biweekly in combination with ara-C, the dose of which was held constant. At a dose of 200 mg/m^2, teniposide induced prolonged severe myelosuppression; hence, a dose of 165 mg/m^2 biweekly has been used in subsequent trials (17). The appropriate doses for adults with leukemia remain to be established. It is not clear, in adults or children, what the maximally tolerated dose of teniposide is in leukemic patients, in whom myelosuppression is an expected toxicity. The importance of this lies in the current use of teniposide as preparative therapy for bone marrow transplantation. Analogy with etoposide in this setting suggests that doses up to four times those used conventionally might be achievable (40); there are no trials currently in progress to address this question.

Intra-arterial teniposide in the treatment of secondary brain metastases seems to be well-tolerated at a dose of 100 mg/m^2 every 3 weeks (41). Toxic effects were drowsiness and seizures. This mode of administration has not been evaluated in a phase I trial, nor has a pharmacologic rationale to establish the relative merit of intra-arterial over iv administration been derived. Future trials of teniposide used in this manner should investigate the tissue extraction of the drug to define the relative advantage of this technique.

Phase II–III Trials

Leukemias

Teniposide has been most extensively evaluated in the leukemias, particularly ALL in children. It was initially evaluated as a single agent in refractory ALL, yielding a cumulative response rate of two of 44 (4%) patients with complete responses (CR) in heavily pretreated patients (42–44). In a similar population with acute nonlymphocytic leukemia, one of 28 (4%) patients had a CR (42,44,45). In spite of the heavy pretreatment of both of these populations, a high proportion of the patients exhibited a reduction in tumor cell burden. Based on the data (16) suggesting synergy with ara-C, and, since ara-C is active in ALL, Rivera et al (46) treated 33 patients refractory to prior therapy, observing nine CR. They then observed nine CR among 14 patients who had failed standard induction therapy, with six of the responders having previously received ara-C (47). These encouraging results led to further development of this regimen; its value in the consolidation of remission has been suggested (48). Recent data from a trial in which teniposide and ara-C have been incorporated with standard agents into the initial therapy of poor-prognosis lymphocytic leukemia and lymphoma are encouraging in that 21 of 25 (84%) pa-

TABLE 3.—Single-agent trials of teniposide in Hodgkin's disease

Dose/schedule	No. of patients— Evaluable	With prior treatment	No. of reponses	Response rate (%)	Comments	Investigator (ref No.)
30 mg/m²/day iv for 1 hr on Days 10-20	22	NS*	1 CR, 5 PR	27	1 CR in stage IIIA (duration, 1 mo)	EORTC (37)
100 mg/m² weekly	9	9	2 PR	22		Chiuten et al (51)
50-100 mg/m² weekly	22	NS	7 PR	32		Mathe et al (52)
40 mg/m² 3 × weekly then 50 mg/m² 2 × weekly	16	13	2 CR, 5 PR	44	1 CR and 2 PR in patients with no prior treatment	Sonntag et al (53)
100 mg/m² weekly	3	3	1 PR	33		Tirelli et al (54)
1-3 mg/kg 2 × weekly	8	8	3 PR	38	All patients heavily pretreated with vinca alkaloids	Dombernowsky et al (55)
Totals	80		3 CR, 23 PR	33		

*NS = not stated.

tients in the former group have had CR (49). Several studies to confirm these data are nearing completion. Teniposide is also active in combination with vincristine and prednisone in refractory ALL: 17 of 53 (31%) patients achieved CR (50).

While it is difficult to determine the true activity of teniposide alone from these studies, its use in combination with ara-C has yielded one of the most promising new regimens in ALL. The role of this regimen will be further clarified by several studies currently in progress, but unequivocal demonstration of its role will require randomized trials. Possible designs include teniposide/ara-C versus standard therapy in consolidation of remission in high-risk pediatric ALL patients, or the addition of teniposide to standard three- or four-drug induction therapy in adult ALL patients.

Lymphoma

Teniposide is an active agent in the treatment of Hodgkin's disease and NHL (tables 3 and 4). In the initial pediatric trials, one partial response (PR) was observed among four patients in each disease category (42). In adults, the cumulative single-agent response rate in pretreated patients has been 26 of 80 (33%) in Hodgkin's disease (37,51-55) and 39 of 126 (31%) in NHL (37,51-54).

Few combination studies have been published in pediatric lymphomas. Dahl et al (49) reported 13 CR in 14 evaluable patients with stages III and IV lymphoblastic NHL treated with teniposide and ara-C followed by standard therapy. A preliminary report of a regimen incorporating teniposide and methotrexate in the maintenance treatment of stages III and IV pediatric NHL has

TABLE 4.—Single-agent trials of teniposide in NHL

Dose/schedule	No. of patients— Evaluable	With prior treatment	No. of responses	Response rate (%)	Comments	Investigator (ref No.)
30 mg/m²/day iv for 1 hr on Days 10-20	44	NS*	19 PR	43	23 reticulosarcoma, 19 lymphosarcoma, 2 reticulosarcoma	EORTC (37)
100 mg/m² weekly	27	27	2 CR, 4 PR	22	—	Chiuten et al (51)
50-100 mg/m² weekly	33	NS	9 PR	27	—	Mathe et al (52)
40 mg/m² 3 × weekly then 50 mg/m² 2 × weekly	7	6	2 PR	29	1 PR in a patient with no prior treatment	Sonntag et al (53)
100 mg/m² weekly	15	14	2 CR, 1 PR	20	1 CR + 1 PR in 5 patients with MF†, all heavily pretreated with vinca alkaloids; 1 CR in untreated patient with histiocytic lymphoma	Tirelli et al (54)
Totals	126	47	4 CR, 35 PR	31		

*NS = not stated.
†MF = mycosis fungoides.

been published (56): the median duration of remission has not yet been reached, but after median follow-up of 40 months, 76% of the patients are projected to be in continuing complete remission at 4 years.

In adult NHL, several regimens incorporating teniposide have been evaluated in a phase II fashion (table 5). The earliest of these, by Missett et al (57), added teniposide to cyclophosphamide, doxorubicin, and prednisone. Although 11 of the patients had relapsed from prior treatment, the 76% total response rate is of the order to be expected from standard treatment in patients without prior chemotherapy. The period of follow-up was insufficient to evaluate response duration. More recently, Lachant et al (58) reported on a Cancer and Leukemia Group B trial in 27 patients relapsing from initial therapy: there were 12 CR and two PR to a regimen incorporating methotrexate, teniposide, procarbazine, and dexamethasone. The high number of CRs in this study suggests that further evaluation of the regimen in comparative trials is warranted.

Several comparative trials of regimens involving teniposide have been conducted; only two have focused on teniposide (table 6). The Australian and New Zealand Cooperative Trial (61) suggests that in 80 relapsed patients, the substitution of teniposide for vincristine in the regimen of cyclophosphamide, vincristine, and prednisone (COP) may reduce toxicity without affecting response rates. Although the trial of Chauvergne et al (62) does not suggest that teniposide has an advantage over doxorubicin added to COP (62), the results are inconclusive because of the small number of patients. The combination of teniposide and mitoguazone was recently investigated by Warrell et al (59) and was chosen based on the single-agent activity of each drug alone in lymphoma (response rates ranging from 20% to 40%) (37,42,51-54,65) and the nonoverlapping toxic effects of each agent. Thirty-one patients with NHL, all heavily pretreated, were evaluable for response. Ten PR were attained for a response rate of 32%. The combination does not appear to be superior to mitoguazone alone, which produced a response rate of 37% in an earlier study by this group (65).

From the available data, a few conclusions are possible. First, teniposide does appear to be active in lymphoma, both Hodgkin's disease and NHL, although definition of response rates by subgroup is not possible. Second, combinations involving teniposide are at an early stage of evaluation in Hodgkin's disease and pediatric NHL. Third, combinations including teniposide have activity in patients with NHL who have relapsed from initial therapy. However, as in ALL, there is no clear indication of how teniposide may be incorporated in the standard treatment of these diseases. It must be considered as an important agent to be incorporated in any regimen noncross-resistant to standard initial therapy. However, it would probably require an additive randomized trial (eg, CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone] vs CHOP-teniposide) in unpretreated patients to isolate definitively its impact on survival.

Neuroblastomas

Stimulated by the encouraging results in the original broad phase II trial (42), Rivera et al (66) performed a straight phase II trial of teniposide in neuroblastoma; a cumulative response rate of 34% was obtained with quite

TABLE 5.—Teniposide-containing combinations in adult lymphomas

Regimen*	Dose/schedule of teniposide	No. of patients— Evaluable	With prior treatment	No. of responses	Response rate (%)	Comments	Investigator (ref No.)
			Non-Hodgkins lymphoma				
MTX + teniposide + procarbazine + dexamethasone	100 mg/m² iv on Days 2, 9	29	29	12 CR, 2 PR	48		Lachant et al (58)
MGBG + teniposide	100 mg/m²	31	31	10 PR	32	Median duration response = 3½ mos	Warrell et al (65)
Teniposide + ADR + Bleo + Pred	40 mg/m² on Days 1, 2 every 21 days	17	17	1 CR, 6 PR	41	Secondary treatment	Goldhirsh et al (60)
ADR + teniposide + CTX	60 mg/m² on Days 3, 4 every 15-21 days	34	11	16 CR, 10 PR	76	Disseminated lymphosarcoma and reticulosarcoma	Missett et al (57)
			Hodgkin's disease				
Teniposide + ADR + Bleo + Pred	40 mg/m² on Days 1, 2	15	15	4 PR	27		Goldhirsh et al (60)
MGBG + teniposide	100 mg/m²	12	12	6 PR	50		Warrell et al (59)

* MTX = methotrexate, MGBG = mitoguazone, ADR = doxorubicin, Bleo = bleomycin, Pred = prednisone, and CTX = cyclophosphamide.

TABLE 6.—Comparative trials of teniposide-containing combinations in adult lymphomas

Combination/ comparison*	Dose/schedule of teniposide	No. of patients— Evaluable	With prior treatment	No. of responses	Response rate (%)	Comments	Investigator (ref No.)
Teniposide + Bleo + ADR	60 mg/m² iv on Days 1, 10	22	5 (ADR)	6 CR, 5 PR	50	$P = 0.024$	Kaplan et al (63)
(vs)							
Teniposide + Bleo + DDP			11 (ADR)	1 CR	9	MST† = 11.5 mos for responders	
CTX + teniposide + Pred (CTP)	100 mg/m² iv × 1 every 3 wks	80	28	35 CR, 23 PR	72	Includes 21 favorable histology, 59 unfavorable	Australian Coop (61)
(vs)							
CTX + VCR + Pred (COP) (randomized)		80	31	37 CR, 24 PR	76	26 favorable, 54 unfavorable, 12% neurotoxicity on this arm	
CTX + VCR + Pred + teniposide	70 mg/m² on Days 5, 12, 19	18	NS‡	5 CR, 7 PR	67		Chauvergne et al (62)
(vs)							
CTX + VCR + Pred + ADR		15	NS	7 CR, 5 PR	80		
Teniposide + DDP + Pred (V-Plat)	NS	46§	46	3 CR, 6 PR	20		O'Connell et al (64)
(vs)							
Teniposide + HMM + Pred (V-Hex) (randomized)		51§		1 CR, 3 PR	8		

*Bleo = bleomycin, ADR = doxorubicin, DDP = cisplatin, CTX = cyclophosphamide, Pred = prednisone, VCR = vincristine, and HMM = hexamethylmelamine.

†MST = median survival time.

‡NS = not stated.

§Includes 8 patients with Hodgkin's disease.

similar schedules (table 7). Since cisplatin is also active as a single agent (response rate of approximately 45%) in this disease (67–70), a trial of the two drugs in combination was performed. Hayes et al (71) obtained a 68% response rate (six CR and nine PR in 22 resistant patients) with cisplatin (90 mg/m²) followed 48 hours later by teniposide (100 mg/m²). The sequence was based on in vitro cytokinetic data. This high response rate was not confirmed in a Children's Cancer Study Group trial (72) in which the scheduling of teniposide and cisplatin was assessed: one arm received cisplatin on Day 1 and teniposide on Day 2; patients on the other arm received the drugs in reverse order. Of 78 patients entered, 21 were evaluable on the first arm and 36 were evaluable on the second arm. The response rates were 38% (one CR and seven PR of 21 patients) in the former and 31% (11 PR of 36 patients) in the latter. Apart from the scheduling of the agents, the more intensive pretreatment undergone by these patients may underlie the lower response rates relative to the St. Jude trial, in which doxorubicin and cyclophosphamide were the only agents used in initial therapy. Studies to refine the use of teniposide alone, and that of the combination, are nearing completion at several institutions. It seems clear, however, that teniposide is an active agent in the treatment of neuroblastoma. The postulated synergy with cisplatin awaits confirmation: its demonstration may be possible only in randomized trials incorporating the agents in the initial therapy of neuroblastoma patients.

Brain Tumors

While early pharmacokinetic studies demonstrated poor penetration of teniposide to the cerebrospinal fluid at levels < 1% of plasma values (28), early clinical trials suggested a significant level of activity in primary brain tumors of adults (73–76). The cumulative response rate spanning four trials was 29% in 63 patients. Despite the heterogeneity of both the histologic diagnosis and response criteria, nonetheless, since few drugs provide evidence of improvement by any criteria in these disorders, these data are at least encouraging. The recent finding of significant levels of teniposide in various samples of brain tumor tissue (34) lends weight to such data.

Studies of intracerebrally implanted tumors in animal models showed that the addition of lomustine and doxorubicin enhanced response rates to teniposide (77,78). Clinical trials of combinations were undertaken, again with significant response rates (table 8). The study of Pouillart et al (78) is particularly significant in terms of

TABLE 7.—Teniposide in neuroblastoma—single-agent activity

Dose/schedule of teniposide	No. of patients— Evaluable	With prior treatment	No. of responses	Response rate (%)	Investigator (ref No.)
100 mg/m^2 2 × weekly (total dose = 175–800 mg/m^2)	7	7	3 PR	43	Rivera et al (66)
130–180 mg/m^2 iv weekly	31	31	1 CR, 9 PR	32	Bleyer et al (42)
Totals	38	38	1 CR, 12 PR	34	

primary brain neoplasms. Of 43 patients with malignant glioma, assessed where possible with radionuclide scanning, 31 (70%) showed regressions lasting ≥ 2 months. None of the patients had previous chemotherapy. These results would seem to argue for (*a*) a confirmatory study in the United States, possibly substituting carmustine for lomustine, and (*b*) a randomized trial of the combination against carmustine in patients with no prior chemotherapy. The latter would be most desirable, since due to the lack of reliable and reproducible response criteria, the use of historical controls is least satisfactory in this disease, and since the study could be tailored to address the most important issue, improvement of survival.

Pediatric brain tumors were included in the broad phase II study: of 11 evaluable patients, there were no objective responses, although two patients had stable disease (42). A Pediatric Oncology Group trial demonstrated no responses among 17 patients (39). However, 12 of those patients had been previously treated, and the group comprised a mixture of six histologic types. Further studies in this age group have not been conducted.

Colon

The activity of teniposide as a single agent in colon cancer has not been well-defined. Two broad phase II trials (45,73) included 20 patients with colon cancer of unknown prior treatment status. There were two responses, for a total response of 10%. While this was not very interesting in itself, a report from Wampler et al (81) followed in which seven of 25 (28%) patients responded to a combination of teniposide and 5-FU. The quality and the duration of the responses were emphasized (median survival of 37+ weeks for the whole group, and 52 weeks for seven patients with gross hepatomegaly). The investigators proceeded to a study of teniposide + 5-FU + mitomycin, as recently reported (82). Thirty-nine of 50 patients were evaluable. Of 21 patients with measurable disease, there were one CR and ten PR (52%); of 18 with evaluable disease, ten responded (56%).

TABLE 8.—Combinations with teniposide in adult brain tumors

Combination*	Dose/schedule of teniposide	No. of evaluable patients†	Prior treatment	No. of Responses	Response rate (%)	Comments‡	Investigator (ref No.)
MeCCNU + teniposide + cranial irradiation	100 mg/m^2 weekly	GB: 7 MA: 9 CA: 4 CNS L: 1 GG: 1 Total: 22	None	3 PR	14	Significant toxicity (myelosuppression); MD:13 STG 1: 9	Gutin and Walker (79)
ADR + CCNU + teniposide	60 mg/m^2 × 2 days	MG: 43 MB: 2 CD: 2 MS: 30 Total: 77		31 patients had regression for ≥ 2 mos	20	Response criteria not defined	Pouillart et al (78)
ADR + CCNU + teniposide	50 mg/m^2 on Days 2, 3, 4	32	NS§	16 PR	50	All patients had CNS metastases; survival: 11.6 + mos; 22 lung 11 breast	Conte et al (80)

*MeCCNU = semustine, ADR = doxorubicin, and CCNU = lomustine.

†GB = glioblastoma, MA = malignant astrocytoma, CA = cerebral astrocytoma, CNS L = CNS lymphoma, GG = ganglioglioma, MG = malignant glioma, MB = medulloblastoma, CD = chordoma, and MS = metastasis.

‡MD = measurable disease, STG 1 = stage 1.

§NS = not stated.

Median survival had not yet been reached. Trials are in progress to confirm these data; however, there is still a need for a randomized trial to more fully define the role of teniposide in carcinoma of the colon.

Other Tumors

Teniposide appears to have some activity in small cell lung cancer: overall, there have been two CR and nine PR in 62 patients (18%), 49 of whom had prior treatment (73,83–85). At the relatively high dose of 100 mg/m^2/day × 5, Aabo et al (83) treated 24 patients, 18 of whom had relapsed from etoposide-containing regimens. One of those 18 patients and two without prior etoposide responded (12.5%). Since even active drugs may achieve low response rates in relapsed small cell lung cancer (86), these data are interesting. In the non-small cell variety, only 4% of 96 patients responded (73,84,87,88); seven were previously treated. Madajewicz et al (41) obtained two CR and three PR in ten patients with brain metastases from adenocarcinoma of the lung, using intra-arterial teniposide as referred to above.

Although responses to teniposide had been seen in bladder cancer in phase I trials (89,90), this promise has not been borne out in single-agent (91) or combination (92,93) studies to date. The suggestion of activity in breast cancer in the study by Spremulli et al (73) has not been pursued. In melanoma (94) and sarcomas (95), small phase II trials of teniposide have shown no activity.

Toxic Effects

The qualitative toxic effects of teniposide were accurately described for the most part in the initial phase I trials. At every schedule tested, the major toxicity has been myelosuppression, which increases with drug dose in a gradual fashion. For example, at 67 mg/m^2 weekly, the majority of patients did not manifest wbc counts $< 2000/mm^3$ (35), while at 165 mg/m^2 twice weekly in patients with leukemia, aplasia of the marrow for approximately 2 weeks was seen (17). The period of aplasia was prolonged by increasing the dose further to 200 mg/m^2 (17). The wide variation in such toxicity among individuals is illustrated by the Southwest Oncology Group trial, in which at 45 mg/m^2, some 31% of the patients experienced grade 4 marrow toxicity, while 60% had only grade 0 or 1 (39).

Other toxic effects have been considerably less frequent. The hypotension associated with rapid infusion of teniposide was described early (35), and is not seen with administration over 30–60 minutes. Hypotension may, however, be a part of the syndrome of hypersensitivity which has been described in up to 10% of patients (96). Bronchospasm, flushing, and urticaria may all be seen with this reaction, which, although usually self-limited, resolving with interruption of the infusion, has been treated with diphenhydramine and hydrocortisone. Such reactions usually occur after repeated administration, but may be manifest on the first dose (96). Believed to have an underlying immunological mechanism, the ubiquity of the plants from which the drug derives might account for the latter phenomenon. Another possibility is a direct reaction to the organic compounds in which teniposide is formulated: such symptoms have been described with other drugs similarly reconstituted (96). None of the hypersensitivity reactions reported to date has been fatal.

In phase II trials, nausea and vomiting of moderate degree have been reported in 5%–19% of patients (97). Alopecia is described in 3%–9% of patients (97). Two cases of elevation of liver enzymes have been reported (97).

CONCLUSIONS

Evidence from the studies reviewed here suggests that teniposide is an active antitumor agent, with particular efficacy in ALL and neuroblastoma in children, and in NHL and brain tumors in adults. The data are flawed by the absence of conclusive trials in these malignancies. For example, it has not been established that a teniposide/ara-C combination is better than ara-C alone in ALL, nor that a teniposide/cisplatin combination is better than cisplatin alone in neuroblastoma. With a single exception, the role of teniposide in the many combinations being used for NHL and Hodgkin's disease remains conjectural. Until this role has been reliably defined in the relevant tumor types, progress in the development of teniposide will be slow. It is of little value to look back and criticize per se the inadequacies of the clinical evaluation of teniposide. Besides the influences of investigator bias and the concurrent introduction of its analog, etoposide, the period spanned by these clinical trials encompasses that in which the principles for the development of new anticancer drugs have been laid down. In attempting prospectively to design trials which would resolve these issues, one is hampered by these inadequacies. How much enthusiasm could be generated for a randomized trial of teniposide/ara-C versus ara-C alone in relapsed childhood ALL?

Notwithstanding these difficulties, we believe that the results of trials to date argue strongly for a renewed development effort for this drug. In tumors other than ALL, the appropriate trials should be feasible. These trials should not, however, address teniposide in isolation. It is equally important to describe its activity relative to etoposide, and, on this basis, to determine in several tumors if teniposide is a useful epipodophyllotoxin in its own right. In this way, one could avoid a profusion of analogs of undetermined value, such as has occurred with the nitrosoureas.

Several questions have to be asked of the epipodophyl-

lotoxin analogs: are they indeed different in their activity in specific tumors? does one have a biochemical or pharmacologic advantage? are they totally cross-resistant? Trials in NHL, small cell lung cancer, and acute myeloblastic leukemia could best address these topics.

Loike (98) has discussed the structure-activity relationships of the podophyllotoxin derivatives. It is certain that "second generation" compounds will be developed for clinical testing. This evaluation would be greatly facilitated, and many unnecessary trials avoided, should the relative merits of the original drugs be clearly defined.

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Study of Erythrocyte Mean Corpuscular Volume During Cytotoxic Therapy as a Predictive Parameter of the Risk of Secondary Leukemia in Hodgkin's Disease[1]

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Erythrocyte mean corpuscular volume (MCV) evolution was studied during cytotoxic therapy in 12 patients with Hodgkin's disease who developed secondary acute leukemia and in 83 patients with Hodgkin's disease without secondary leukemia as control group. Significant differences were observed in the maximum MCV and in the MCV maximum increase during therapy between the two groups of patients. These differences remained significant between the patients treated with chemotherapy alone and those treated with chemotherapy and radiotherapy. MCV maximum increase > 23.9 fl was observed in all patients with secondary leukemia and in only 20% of those without secondary leukemia; it was reached 46.3 months before the first sign of preleukemia. Its value in predicting the leukemic risk in Hodgkin's disease is discussed. [Cancer Treat Rep 68:1467–1470, 1984]

Secondary leukemia following cytotoxic therapy is more frequent in Hodgkin's disease than in any other cancer. In 1980, 301 cases had been reported (1). Its incidence ranges from 1.5% to 3.9% at 5 years (2,3). The highest frequency reported today is 9.9% at 9 years (3). The leukemic risk seems linked with therapy since most cases occurred among patients treated with chemotherapy and radiotherapy in combination (1).

By reviewing the charts of some cases of leukemia after Hodgkin's disease, we have been impressed by the variations of the mean corpuscular volume (MCV) towards very high value during cytotoxic therapy in several of these cases. We wondered whether such increases in MCV could be a reflection of the intensity of the damage imposed on the stem cell by the therapy of Hodgkin's disease. Should this be the case, the evolution of the MCV could be different during therapy between patients with Hodgkin's disease who developed secondary leukemia and patients in whom this complication will not occur.

To test this hypothesis, we studied the MCV variations during cytotoxic therapy in patients with Hodgkin's disease followed by or not followed by secondary acute leukemia.

PATIENTS AND METHODS

MCV evolution during cytotoxic therapy was studied in 83 patients with Hodgkin's disease who had not developed secondary leukemia and in 12 patients in whom secondary leukemia occurred. Maximum MCV was the highest MCV reached during therapy or in the first 6 months after therapy completion. MCV maximum increase was the difference between the MCV at onset of Hodgkin's disease and the maximum MCV. Maximum MCV and MCV maximum increase were considered only in patients who had monthly hemogram with MCV determination during therapy. Macrocytosis was defined as a MCV > 100 fl. MCV was measured with a Coulter Counter Model S or S plus II.

The patients with Hodgkin's disease not followed by secondary leukemia were all of those diagnosed between 1975 and 1980 in the Departments of Hematology of the Hospitals Enfant-Jesus and Hotel-Dieu (Quebec City, Canada). Five patients who had incomplete data, one with macrocytosis prior to therapy, and one who received multiple transfusions during therapy were excluded. Of the 83 remaining patients, mean age at diagnosis of Hodgkin's disease was 33 ± 15.8 years. Seventeen patients had stage I Hodgkin's disease, 24 had stage II, 19 had stage III, 19 had stage IV, and initial staging was not known in four. Eleven patients died of their disease. Median follow-up time was 56 months.

We studied 16 patients with Hodgkin's disease with secondary leukemia from five different hospitals. However, four patients could not be included in this study: hemograms during therapy were not available in one pa-

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tient; MCV measures were lacking at the end of therapy in two patients whose MCV reached 106 and 107 fl before therapy completion; and multiple transfusions during therapy were administered to one patient whose MCV reached 98 fl.

The 12 remaining patients with Hodgkin's disease had a mean age of 33.9 ± 12.6 years. Two patients had stage I_A Hodgkin's disease, one had stage II_B, two had stage III_A, four had stage IV_A, and one had stage IV_B. Eight patients had relapse of their disease and four remained disease-free before the onset of preleukemia or secondary leukemia. Patient 2 developed refractory anemia with excess of blasts (RAEB) and Patient 9 developed refractory anemia according to FAB criteria (4), both with nonrandom chromosome abnormalities. Patient 10 had undifferentiated acute leukemia. Their main characteristics are summarized in table 1. Initial MCV was not available in Patient 8.

Patients were divided in three groups according to therapy. Patients in group 1 received radiotherapy alone, those in group 2 received MOPP and maintenance therapy (trimestrial MOPP, vinblastine, or cyclophosphamide), and those in group 3 received MOPP and radiotherapy and, in some cases, maintenance therapy. Patient 9 with secondary leukemia received only one course of MOPP before radiotherapy and was classified in group 1. Eleven patients among those who did not develop secondary leukemia, who received induction MOPP only or other chemotherapy regimens, did not belong to these groups. Their maximum MCV was 98.7 ± 10.9 fl and their MCV maximum increase was 16 ± 7.6 fl. Median duration of chemotherapy was 25.8 ± 10.8 months in group 2 and 16.9 ± 11.5 months in group 3.

Statistical tests used were Student's t test and correlation coefficient.

RESULTS

The maximum MCV was 99.8 ± 14.7 fl and the MCV maximum increase was 16.2 ± 8.4 fl in patients without secondary leukemia. In patients with secondary leukemia, the maximum MCV was 112.6 ± 7.1 fl and the MCV maximum increase was 30.1 ± 7.4 fl. Differences were statistically significant. In patients of groups 2 and 3, differences remained significant but appeared larger for the MCV maximum increase than for the maximum MCV. Table 2 shows the maximum MCV and the MCV maximum increase in each group. Maximum MCV and MCV maximum increase during therapy were correlated in patients without secondary leukemia ($r = 0.64$; $P < 0.001$), as well as in patients who developed secondary leukemia ($r = 0.82$; $P < 0.01$). Figure 1 shows the maximum MCV and the MCV maximum increase for all patients. The duration of macrocytosis in patients with-

TABLE 1.—Characteristics of patients with Hodgkin's disease followed by secondary leukemia

Patient No.	Sex/age (yrs)	Therapy*	Chemotherapy duration (mos)	Preleukemia (mos from Hodgkin's disease diagnosis)	Leukemia (mos from Hodgkin's disease diagnosis)
1	F/31	MOPP, MOPP(M)	27	—	Myeloblastic (59)
2	M/21	MOPP, CY, MOPP, CY, RT, MOPP-Bleo	47	Pancytopenia (109)	Nonrandom chromosome abnormalities
3	M/31	MOPP, CY, RT, CY, RT, CY, MOPP-Bleo, ABVD	60	Anemia (107)	Myeloblastic (116)
4	F/55	MOPP, MOPP(M), RT, MOPP-Bleo, Bleo, CVPP, RT	29	Pancytopenia (48)	Myelomonocytic (51)
5	M/46	MOPP, Velbe, CY, RT, MOPP, CY	90	Macrocytosis (107)	Myeloblastic (117)
6	M/43	RT, MOPP, CY, MOPP(M)	24	Macrocytic anemia (41)	Monoblastic (63)
7	M/58	MOPP, CY, Velbe, CY	32	Macrocytosis-thrombopenia (37)	Myelomonocytic (49)
8	M/39	RT, RT, MOPP, MOPP(M), MOPP-Bleo, RT	33	Peripheral myeloblastosis (76)	Myelomonocytic (78)
9	M/22	MOPP, RT	1	Anemia-leukopenia (76)	Nonrandom chromosome abnormalities (173)
10	M/35	NH_2, RT, CLB, CY, RT, Velbe, PCZ, CY, PCZ	90	Pancytopenia (154)	
11	F/28	MOPP, RT	3	Thrombopenia (59)	Myeloblastic (63)
12	M/22	MOPP, MOPP(M), MOPP, BCNU, CY	70	Myelemia (108)	Myelomonocytic (113)

*MOPP = mechlorethamine (NH_2), vincristine, procarbazine (PCZ), and prednisone; MOPP(M) = MOPP maintenance; CY = cyclophosphamide; RT = radiotherapy; Bleo = bleomycin; ABVD = doxorubicin, bleomycin, vincristine, and dacarbazine; CVPP = cyclophosphamide, vincristine, procarbazine, and prednisone; Velbe = vinblastine; CLB = chlorambucil; and BCNU = carmustine.

out secondary leukemia who became macrocytic on therapy was 20.5 ± 19.2 months and in patients with secondary leukemia was 25.9 ± 15 months. However, this difference was not significant ($t_{34} = 0.85$).

MCV maximum increase of > 24 fl was observed in all patients with secondary leukemia. Among the 13 patients without secondary leukemia with a MCV maximum increase of > 24 fl, five were male and eight were female, and their mean age of 33.1 ± 12.1 years was not different from the mean age of the patients with a MCV maximum increase of < 24 fl. In seven patients it occurred just after induction therapy and in six patients it occurred during maintenance therapy. Median follow-up time was 60 months.

In patients with secondary leukemia, MCV maximum increase was reached during the initial chemotherapy in five patients and during relapse in the remaining seven. Duration of chemotherapy was 22.0 ± 19 months (range, 1-58) when MCV reached its highest value. MCV maximum increase was observed 46.3 ± 24 months before the first hematologic sign of preleukemia and 53.4 ± 26.4 months before frank acute leukemia. Hemograms corresponding to the maximum MCV were normal in five patients and showed moderate anemia in two, anemia and thrombopenia in three, moderate leukopenia in one, and leukopenia with thrombopenia in one. After reaching the maximum, MCV returned to a normal value (87-97 fl) in six of these patients, while the other six remained macrocytic until the first signs of leukemia or preleukemia. Median follow-up time from diagnosis of Hodgkin's disease to preleukemia was 82 months.

DISCUSSION

The intensity of the metabolic changes in the erythrocytic cells during cytotoxic therapy, which is reflected in the MCV increase, seems proportional to the leukemic risk in Hodgkin's disease. The maximum MCV increase, as well as the maximum MCV, which were reached during cytotoxic therapy appeared higher in the patients who developed secondary leukemia than in the other patients with Hodgkin's disease.

The factors which are known to increase the leukemic risk in Hodgkin's disease are stage IV, heavy therapy with radiotherapy and chemotherapy in combination, recurrence after MOPP, and > 40 years of age (1,3,5). On the contrary, patients who received only radiotherapy do not seem to be at high risk of secondary leukemia (2,3,6,7). No relation was demonstrated between the leukemic risk and the bone marrow toxicity after combination drug induction regimen as judged by hemoglobin level, leukocyte count, and platelet count (3).

MCV maximum increase during therapy might well be a valuable predictive factor of the leukemic risk in Hodgkin's disease. It is easy to perform, it can be done in most patients who do not need transfusions, and it occurs many years before the first signs of preleukemia. The MCV maximum increase according to therapy correlates well with the leukemic risk. Inside our control group of heavily treated patients, one-third had an increase of > 24 fl, which is the minimum increase observed in the cases of secondary leukemia. These patients can be considered to have a high risk of secondary leukemia since their mean follow-up was only 4.7 years. On the contrary, most patients with a slight MCV increase during therapy can be considered to have a low risk of secondary leukemia.

In vitro agar cultures and cytogenetic studies performed in patients with secondary cytopenia or peripheral blood abnormalities can lead to an early diagnosis of preleukemia (8-10). Macrocytosis which appears after therapy completion has been recognized as an early sign of preleukemia (11). It is of interest to determine whether the patients with a high MCV increase on therapy already have the features of preleukemia with these procedures or will have these just before the clinical onset. Should future studies confirm the value of the MCV maximum increase in identifying patients at risk of

TABLE 2.—Maximum MCV and MCV maximum increase during cytotoxic therapy in patients with Hodgkin's disease followed by or not followed by secondary leukemia (SL) *

	Maximum MCV (fl)		MCV maximum increase (fl)	
All patients without SL	99.8 ± 14.7	$t_{88} = 2.95$	16.2 ± 8.4	$t_{82} = 5.36$
All patients with SL	112.6 ± 7.1	$P < 0.01$	30.1 ± 7.4	$P < 0.001$
Group 1 without SL	94.1 ± 5.4		8.6 ± 3	
Group 1 with SL†	106.5†		23.9†	
Group 2 without SL	102 ± 8.4	$t_{22} = 2.02$	18.8 ± 7.4	$t_{21} = 2.65$
Group 2 with SL	111 ± 5.9	$P \sim 0.05$	31.1 ± 7.9	$P < 0.02$
Group 3 without SL	105.6 ± 7.8	$t_{23} = 2.42$	18.9 ± 7.8	$t_{23} = 3.80$
Group 3 with SL	114.3 ± 8	$P < 0.05$	31.9 ± 7.4	$P < 0.01$

* Group 1 received radiotherapy only, group 2 received MOPP and maintenance chemotherapy, and group 3 received MOPP and radiotherapy with or without maintenance therapy.

†One patient who received just 1 course of MOPP.

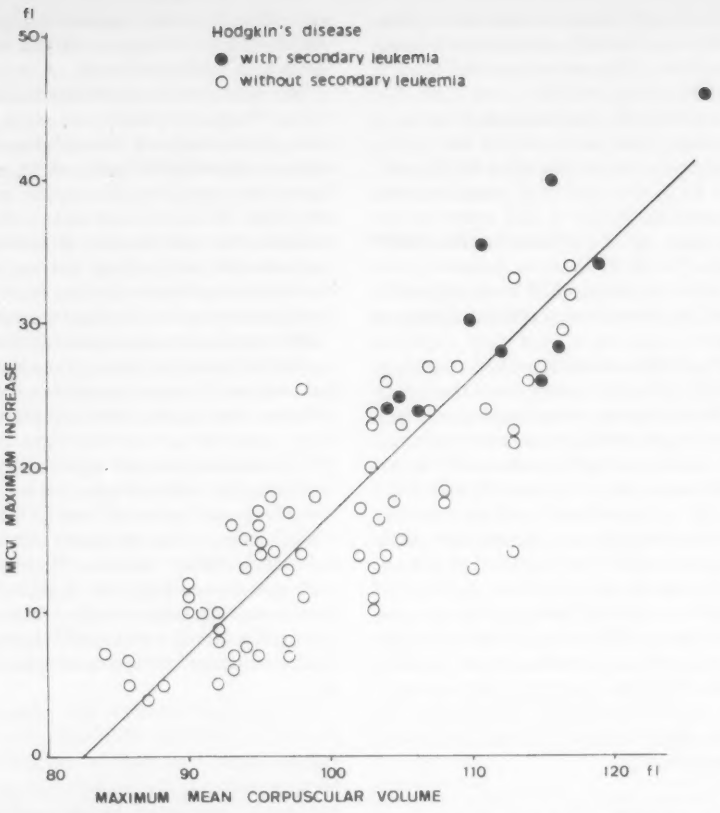

FIGURE 1.—Correlation between the maximum erythrocyte MCV and the MCV maximum increase reached during cytotoxic therapy in patients with Hodgkin's disease followed by or not followed by secondary leukemia.

secondary leukemia in Hodgkin's disease, the therapeutic approach could be modified in view of avoiding or at least limiting the MCV increase. For example, other cytotoxic regimens, such as ABVD, could increase MCV less than MOPP. This attitude could result in a decrease of the incidence of secondary leukemia.

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High-Dose Etoposide for Refractory Malignancies: A Phase I Study[1]

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Etoposide is active against a number of solid tumors when used in a standard dose. The toxicity at a standard dose level is mild myelosuppression without extramedullary toxicity. Recent studies in man support the dose-response relationship of etoposide. In a group of 22 patients with progressive disseminated malignancies, the dose of etoposide was escalated to define dose-limiting extramedullary toxicity, which was oropharyngeal mucositis at a dose level of 3.5 g/m². Bone marrow toxicity was completely reversible. No cumulative toxicity was seen. Partial responses were seen in nine patients. In two of three patients with CNS metastases, improvement was seen. Etoposide is a suitable drug for high-dose chemotherapy. [Cancer Treat Rep 68:1471–1474, 1984]

Etoposide, a semisynthetic podophyllotoxin derivative, is active against a number of solid tumors in a "standard" dose of 200–400 mg/m² (1). This standard dose was determined in phase I studies; dose-limiting toxicity in these studies was myelosuppression of modest degree and short duration (2,3).

Currently in clinical practice, much more severe hematologic toxicity is accepted (eg, in the treatment of acute leukemia and small cell lung cancer [SCLC]). This is due to the possibilities of improved supportive care, including prevention from infection (4), platelet transfusion, and feeding (5,6). From various experimental in vivo studies, there is evidence that for most cytostatic drugs, a positive dose-response relationship can occur at dose levels above the standard dose (7).

Etoposide is an ideal drug for a dose augmentation study, because increasing the dose up to 1.5 g/m² in patients with acute leukemia resulted in temporary myelosuppression and mild extramedullary toxicity (8). Furthermore, a dose-dependent activity against Lewis lung carcinoma and a human leukemic lymphoblast cell line was found in vitro (9,10), while in vivo data suggest a dose-response relationship in patients with germ cell malignancies (11) and SCLC (12).

At a standard dose, the activity of etoposide seems to be schedule-dependent (13); therefore, etoposide is generally given in a fractionated schedule. The optimal way of fractionation is unknown. To evaluate more extensively the dose-limiting toxicity, we started a phase I study of etoposide administered iv two times a day for 3 consecutive days.

MATERIALS AND METHODS

Patients

From November 1982 to September 1983, 22 patients with disseminated malignancies were entered in a phase I study with high-dose etoposide. Criteria for eligibility in the study were: age < 70 years, leukocyte count ⩾ 3.0 × 10^9/L, platelet count ⩾ 100 x 10^9/L, no signs of bone marrow involvement, Karnofsky score ⩾ 50, normal renal function (serum creatinine ⩽ 150 μmols/L), normal bilirubin (⩽ 25 μmols/L), and no effective therapy available. Informed consent was obtained for all patients.

Etoposide Administration

Etoposide was diluted in normal saline to a maximum concentration of 0.8 mg/ml and administered iv in 1 hour. Single doses > 800 mg were given in 1.5 hours over 3 consecutive days with six infusions of equal amounts at 12-hour intervals.

The starting dose of this study was 1.0 g/m². Dose escalations were 0.5 g/m², and were to proceed if no unacceptable toxicity was seen in any of three patients at that level. Unacceptable toxicity, using the World Health Organization (WHO) grading system (14), was defined as oral

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TABLE 1.—Grading of observed toxic effects*

Toxic effect	Grade — 0	1	2	3	4
Oral	No change	Soreness/erythema	Erythema, ulcers, can eat solids	Ulcers, requiring liquid diet only	Alimentation not possible
Diarrhea	None	Transient, ⩽ 2 days	Tolerable, but > 2 days	Intolerable, requiring therapy	Hemorrhagic dehydration
Cutaneous	No change	Erythema	Dry desquamation, vesiculation, pruritis	Moist desquamation, ulceration	Exfoliative dermatitis, necrosis requiring surgical intervention
Neurotoxicity	None	Paresthesias and/or decreased tendon reflexes	Severe paresthesias and/or mild weakness	Intolerable paresthesias and/or marked motor loss	Paralysis

* Grades are according to WHO criteria (ref 14).

mucositis (grade 4), diarrhea (grade 3), dermatitis (grade 4), and neurotoxicity (grade 3) (table 1). To be evaluable for toxicity, the patient had to survive for at least 4 weeks after the start of treatment.

All patients received etoposide on an inpatient basis. Selective decontamination of the digestive tract (4) with oral antibiotics and oral amphotericin B was used to prevent infection. Platelet transfusions were given when bleeding was present or prophylactically if the thrombocyte count was $< 15 \times 10^9$/L. Infection days were defined as days with fever ⩾ 38.5°C (axillary) and the presence of either clinically or bacteriologically documented infections.

If no disease progression was present and no unacceptable toxicity was seen, the patient was treated with another course in the same dosage.

Response

To be evaluable for response, the patient had to be followed up at least 4 weeks after the start of treatment.

Complete remission was defined as the disappearance of all signs and symptoms of detectable tumor. Partial remission was defined as a decrease in the size of at least 50% of the sum of the products of the largest perpendicular diameters of measurable lesions. If a decrease in the level of an established tumor marker (eg, $alpha_1$-fetoprotein or beta-human chorionic gonadotropin) of > 90% was seen in patients without measurable or evaluable lesions, this was also considered a partial response. Minor response was defined as a decrease of a measurable lesion between 25% and 50%. Stable disease was defined as a decrease or increase of a measurable lesion < 25%. Disease progression was defined as the growth of measurable lesions. Subjective response was defined as improvement of neurological symptoms of CNS metastases, improvement of dyspnea due to pulmonary lymphangitis, improvement of pain due to tumor involvement, and normalization of hypercalcemia.

RESULTS

Patients

Of 22 patients entered in the study, there were 15 males and seven females, with a mean age of 47 years (range, 21–69). Nineteen patients were heavily pretreated with combination chemotherapy with or without radiotherapy. In ten patients, the standard dose of etoposide was included in combination chemotherapy. Nine patients received more than one course of etoposide; six of these patients received more than two courses.

Nonhematologic Toxicity

Moderate nausea and vomiting, controllable by antiemetic therapy, was present in 11 patients (50%). Diarrhea did not occur. Mucositis seems to have been dose-related (table 2) and was dose-limiting in one patient after

TABLE 2.—Mucositis

Dose of etoposide (g/m^2)	No. of courses (No. of patients)	Grade* — 0	1	2	3	4
1.0	9 (5)	5	4	—	—	—
1.5	9 (4)	3	5	1	—	—
2.0	10 (4)	2	6	2	—	—
2.5	5 (4)	—	—	4	1	—
3.0	3 (3)	—	1	—	2	—
3.5	2 (2)	—	—	—	1	1

* Grades are according to WHO criteria (ref 14).

3.5 g/m². Mucositis was completely reversible within the period necessary for bone marrow recovery. Routine virological investigations revealed a herpes simplex infection in only three patients. Two of these patients had typical herpes lip lesions, which were different from the mucosal damage seen in the other patients. All patients without alopecia due to prior therapy had hair loss. No neurotoxicity occurred, nor did pre-existing neuropathy due to prior chemotherapy increase. In one patient after the first course of etoposide (2.0 g/m²), skin lesions developed on the neck, thorax, and arms comparable to the recently described Stevens-Johnson syndrome (15). There were no signs of acute or cumulative hepatic toxicity. Somnolence was not seen.

In the patients receiving more than one course, no signs of cumulative toxicity with respect to mucositis or bone marrow function were observed.

In one patient, hypotension and fever were seen shortly after the second infusion (3.0 g/m²); the following four infusions were given slower (2 hours), with no complications.

Hematologic Toxicity (table 3)

The duration and degree of leukopenia and thrombocytopenia did not increase with dose escalation. The moment of bone marrow recovery, defined as a leukocyte count $> 1.0 \times 10^9$/L and a thrombocyte count $> 50 \times 10^9$/L, is not postponed at the highest dose level, although the number of platelet transfusions was slightly increased. In ten of 38 courses, a clinically or bacteriologically documented infection was seen, which responded to antibiotic treatment.

Response (table 4)

Seventeen patients were evaluable for response after one course. There were no complete remissions. Nine patients had partial response, one had a minor response of cutaneous metastases of adenocarcinoma of the lung, and four had stable disease. Two patients had disease progression. One patient with a germ cell tumor had a good partial remission of systemic tumor, but progression of symptoms of meningeal carcinomatosis. In one patient with bone metastases, hypercalcemia normalized for a short period. In two patients without an evaluable tumor lesion, subjective improvement was seen: dyspnea due to pulmonary lymphangitis disappeared in one patient; the second patient had major improvement of pain and pareses due to meningeal carcinomatosis of SCLC for > 6 months.

DISCUSSION

In this study, the dose-limiting toxicity of high-dose etoposide, administered iv on 3 consecutive days, was oropharyngeal mucositis, occurring at 3.5 g/m². The severity of the mucositis seems dose-related, although there is a rather great difference between individuals. The mucositis of the oropharyngeal region could be influenced by a local effect of etoposide in the saliva (16). The influence of herpes simplex on the mucositis is uncertain; our data concerning this aspect seem to exclude an important influence. Wolff et al (17) found dose-limiting mucosal toxicity at a total dose of 2.7 g/m². This dose is lower than the total dose per cycle used in our study. This difference can possibly be explained by the different administration schedules used. Wolff et al used a schedule in which the total dose was divided into three infusions, probably leading to higher peak plasma and saliva levels of etoposide. Clinical signs of mucositis of the lower part of the digestive tract were not seen.

The hematologic toxicity was severe, but not dose-dependent. The duration of leukopenia and thrombocytopenia was not long enough to expect any benefit from autologous bone marrow transplantation (ABMT) as was done by Wolff et al (17). Moreover, the moment of bone marrow recovery in a comparable study using high-dose cyclophosphamide and high-dose etoposide with ABMT (18) was considerably postponed compared to the patients discussed in this study.

Several responses were seen. The assumption that a

TABLE 3.—Hematologic toxicity

Dose of etoposide (g/m²)	No. of courses (No. of patients)	Mean No. of days (range) with leukocyte count* — ⩽ 0.5	⩽ 0.1	Mean No. of days (range) with platelet count ⩽ 20*	Mean No. of platelet transfusions (range)	Mean cycle Day (range)† with leukocyte count > 1.0* and platelet count > 50*	No. of infection days‡
1.0	9 (5)	5.1 (0-10)	0.6 (0-3)	1.0 (0-3)	0.7 (0-2)	19 (17-21)	1.2 (0-4)
1.5	9 (4)	5.0 (0-8)	0	3.1 (1-7)	1.0 (0-2)	19 (19-21)	0.4 (0-3)
2.0	10 (4)	2.4 (0-9)	0.6 (0-6)	3.2 (1-8)	1.8 (1-4)	18 (16-18)	1.8 (1-4)
2.5	5 (4)	5 (1-10)	0.4 (0-1)	3.0 (1-4)	2.0 (1-3)	17 (16-18)	2.2 (0-6)
3.0	3 (3)	10.0 (9-11)	2.0 (1-5)	5.3 (4-7)	2.6 (2-3)	23 (21-26)	3.0 (2-4)
3.5	2 (2)	6.5 (6-7)	2.0 (1-3)	3.5 (3-4)	1.5 (1-2)	17	5.5 (4-7)

* × 10^9 cells/L.
† Day 1 = 1st day of chemotherapy.
‡ Axillary temperature ⩾ 38.5°C.

TABLE 4.—Response after 1 course

Diagnosis	No. of patients*						Duration of response (mos)
	Total	PR	MR	SD	DP	NE	
Breast cancer	4	1			1	2†	3
Adenocarcinoma, lung	1		1				2
Adenocarcinoma, unknown origin	1				1		—
Endometrium carcinoma	1			1			—
Squamous carcinoma, lung	1			1			—
SCLC	7	3		2		2	1, 2, 4
SCLC, CNS metastases only	2	1				1‡	3
Germ cell tumor	5	5§					1, 1, 1.5, 1.5, 2

*PR = partial remission; MR = minor response; SD = stable disease; DP = disease progression; NE = not evaluable.

†Improvement of dyspnea due to pulmonary lymphangitis, normalization of hypercalcemia.

‡Improvement of symptoms due to meningeal carcinomatosis.

§1 patient with mixed response: progression of meningeal carcinomatosis, but regression of tumor elsewhere.

dose-response relationship exists for etoposide is supported by the short-term response seen in a patient with adenocarcinoma of the lung, since the tumor in this patient was progressive during standard-dose etoposide; a nearly partial remission was observed of several cutaneous metastases. Also, the effects seen in three breast cancer patients are promising; although the number of patients is small, the response rate is higher than that expected from standard-dose therapy (8% response rate) (1). An unexpected effect of high-dose etoposide was the response of CNS metastases in two patients with SCLC. Pharmacokinetic studies in these patients showed detectable levels of etoposide in the cerebrospinal fluid (19). In contrast with this is the progression of meningeal carcinomatosis in a patient with a germ cell tumor during a partial response of the tumor elsewhere. The assumed dose-response relationship and the effect against CNS metastases of SCLC make etoposide a suitable drug for incorporation in high-dose regimens. The dose suitable for further phase II studies seems to be 2.5 g/m^2. For studies on an outpatient basis or in combination regimens, 1.5 g/m^2 is probably the highest tolerable dose (18). Pharmacokinetic studies have to be performed to decide whether the administration scheme of etoposide in this study is optimal. Perhaps different schemes, such as continuous infusion, may be more effective.

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Effects of Dose and Duration of Exposure on 5-Aza-2′-deoxycytidine Cytotoxicity for L1210 Leukemia In Vitro[1,2]

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We have investigated the effects of 5-aza-2′-deoxycytidine (DAC) on the growth and clonogenic potential of L1210 leukemia in vitro. Cells were exposed to DAC (0.001–100 μg/ml) for periods of 1–120 hrs. Following drug removal, cell growth in suspension culture was measured for up to 7 days, and cell survival was estimated by a colony-formation assay. When cell clonogenicity was plotted against DAC concentration in log-log axis, curves for each exposure time were linear between 0.01 and 0.5 μg/ml of DAC, but survival leveled off to a constant percentage for drug concentrations > 0.5 μg/ml. Percent survival decreased as exposure time increased up to 24 hrs; however, increases in exposure time > 24 hrs did not consistently decrease survival any further. At the lower concentrations this leveling of cytotoxicity is due to the spontaneous decomposition of DAC and to the lack of cytotoxicity of the breakdown products. At the higher concentrations the cause of the leveling remains uncertain. Incubation of L1210 with DAC at concentrations > 0.5 μg/ml for ≥ 24 hrs resulted in total inhibition of measurable cell growth for 72–96 hrs following drug removal. Sequential colony-formation assays at various intervals following drug removal demonstrated a time-dependent increase in cell clonogenicity at a rate approximating the growth rate of untreated L1210 cells. This suggests that despite total cytostasis of the major population of cells, a small fraction of cells is capable of dividing at a near normal rate if removed from the drug environment. Implications of these results for in vivo applications of DAC are discussed. [Cancer Treat Rep 68:1475–1481, 1984]

The nucleoside analog 5-aza-2′-deoxycytidine (DAC) has been shown to be a potent antineoplastic agent either in vitro (1,2) or in vivo (2–4) against a number of animal tumors including AKR, P388, and L1210 leukemias and hamster fibrosarcoma. DAC is anabolized to the nucleoside monophosphate by deoxycytidine kinase (5) and is ultimately incorporated into DNA in place of dCMP (4). It has been postulated that the cell-killing effects of DAC result from the presence of this chemically unstable nucleoside in DNA (6). In addition, incorporation of DAC residues into DNA leads to inhibition of DNA methyltransferase (7). Methylation of cytosine residues in DNA by this enzyme has been implicated in the control of cellular gene expression and differentiation and the inhibition of this process by DAC has been correlated with cytotoxicity (7–9).

Momparler and Gonzales (2) investigated the effects of DAC administered by iv infusion on the survival of L1210 leukemia-bearing mice. The most effective treatment was an 8-hr infusion at a dose producing an estimated steady-state plasma level of 6.0 μg/ml and resulting in a 272% increase in lifespan (ILS) with an estimated 12.5-log leukemic cell kill. These investigators also reported in vitro cytotoxicity data for 8-hr exposures, in which 0.01–0.2 μg/ml of DAC produced a ½- to 1-log cell kill. The concentration range studied and the cell kill obtained in vitro are markedly lower than those estimated from in vivo experiments. Since the effectiveness of most

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antimetabolites is dependent upon exposure time as well as concentration of drug (10), we have extended the in vitro studies of Momparler and Gonzales to include longer times over a wide range of concentrations. Growth and viability of L1210 were investigated following exposure of cells to DAC concentrations of 0.001–100 μg/ml for 1–120 hrs. The relative contributions of drug concentration and exposure time to cytotoxicity were examined in a way that took into consideration the spontaneous degradation of DAC.

METHODS

Drugs and Chemicals

DAC was kindly provided by Dr. D. de Vos, Pharmachemie, B. V. (Haarlem, Holland) and by the Drug Synthesis and Chemistry Branch, National Cancer Institute (Bethesda, MD). Phosphate-buffered saline (PBS), pH 7.4 (0.15 M NaCl with 1.06 mM KH_2PO_4 and 5.6 mM Na_2HPO_4), was purchased from HEM Research, Inc (Rockville, MD). KH_2PO_4 and $Na_2HPO_4 \cdot 7H_2O$ were purchased from Fisher Scientific Co (Columbia, MD).

High-Performance Liquid Chromatography (HPLC) Analysis of DAC Solutions

The procedure for HPLC determination of DAC was adapted from that of Lin et al (6). An Altex Model 110A solvent delivery pump (Beckman Instruments, Berkeley, CA) was used in conjunction with a Model 420 controller/programmer. Isocratic elution was with 0.01 M KH_2PO_4/Na_2HPO_4 buffer, pH 6.8, at a flow rate of 1 ml/min. Reversed-phase columns used were an Altex Ultrasphere-ODS (4.6 mm inside diameter × 25 cm, Beckman Instruments) and a Brownlee Labs RP-8 (4.6 mm inside diameter × 25 cm, Rheodyne Corp, Berkeley, CA); either column was satisfactory. With the latter column, which was used more extensively, DAC eluted around 9.7 mins. DAC was quantitated by UV absorbance at 240 nm and peak area integration using a Beckman 165 variable wavelength detector and a Chromatopac C-E1B integrator (Shimadzu Corp, Kyoto, Japan). DAC was dissolved in PBS, pH 7.4, and a standard curve prepared. Peak area was linear with concentration from 0.1 to 100 μg/ml of DAC, with a correlation coefficient of 0.999. The sensitivity of the assay is at least 0.1 μg/ml, with a coefficient of variation of 4.3%.

Cell Culture

Mouse L1210 leukemia cells were grown at 37°C in suspension culture in RPMI-1630 medium (HEM Research, Inc), supplemented with 20% heat-inactivated horse serum (GIBCO, Grand Island, NY), 0.84 mM L-glutamine, penicillin (82 units/ml), streptomycin (82 μg/ml), and 0.05 mM mercaptoethanol. Stock cultures were maintained in exponential growth at a density between 0.5 and 10 × 10^5 cells/ml. Periodic testing (Flow Laboratories, McLean, VA) confirmed the absence of mycoplasma in the cell cultures.

Clonogenic and Cell Growth Assays

The effects of DAC on L1210 cell clonogenicity were examined by determining the soft-agar colony-forming ability of treated cells. DAC was dissolved and diluted in PBS (pH 7.4) and added to cell suspensions (0.3 × 10^5 to 7.0 × 10^5 cells/ml) to give a final drug concentration between 0.001 and 100 μg/ml. Unless otherwise indicated, DAC was dissolved and used within 15 mins. After 1–120 hrs incubation at 37°C, the cells were washed three times by centrifugation and resuspended in fresh medium. Cell density was determined using a Coulter Counter (Model ZBI, Coulter Electronics, Hialeah, FL) and appropriate dilutions were made. Aliquots containing 10^2 to 10^5 cells were seeded into plastic tubes (Falcon Plastics #2058, Oxnard, CA) containing RPMI-1630 medium plus 0.1% agar. Following incubation at 37°C for 12–19 days, the number of colonies in each tube was determined by visual counting with a background of fluorescent light and expressed as a percentage of control cloning efficiency. In several experiments, cell clonogenicity was determined as a function of time following drug removal by washing and then incubating cells in drug-free medium and performing colony-formation assays at various intervals up to 5 days after drug exposure.

L1210 growth in suspension culture was also followed for at least 5 days after drug removal by resuspending cells in fresh media and making daily measurements of cell density with the Coulter Counter. Cultures were diluted with fresh medium as required to maintain a density between 0.5 × 10^5 and 10 × 10^5 cells/ml. Nongrowing cultures were also periodically resuspended in fresh medium. Growth curves were generated by plotting N_t/N_o versus time, where N_t is the cell density at time t and N_o is the initial cell density after drug washout.

Cytotoxicity of Stored DAC Solutions

The cytotoxic activity of freshly prepared DAC solutions was determined as described above (17.5-hr exposure). These solutions were then stored at 37°C for 8 days and the cytotoxicity assay was repeated. Actual DAC content of fresh and stored solutions was determined by HPLC as described above.

Degradation of DAC in RPMI-1630

Freshly prepared DAC was diluted into flasks containing RPMI-1630 medium (with and without L1210 cells) to give final concentrations of 10 and 100 μg/ml. Flasks

were incubated at 37°C for 48 hrs. Aliquots of medium were removed at various times and those containing L1210 cells were filtered using the centrifree micropartition system (Amicon Corp, Bedford, MA). DAC content was then determined by HPLC.

DAC concentration was plotted versus time and the half-life of the apparent first-order degradation was calculated by regression analysis.

Calculation of Area Under DAC Exposure Curves

DAC is unstable in aqueous solution and decomposes in a temperature- and pH-dependent manner to form *N*-(formylamidino)-*N'*-β-D-2-deoxyribofuranosylurea, 1-β-D-2'-deoxyribofuranosyl-3-guanylurea, plus other unidentified products (6). Preliminary experiments demonstrated that in RPMI-1630 medium at 37°C, DAC decomposed in a first-order fashion with a half-life of 17.5 hrs in cell-free medium and 15.2 hrs in medium containing L1210 cells. To account for the constantly decreasing concentrations of DAC that would take place during cell incubations at 37°C, total area under the concentration × time (C × t) exposure curves was calculated as:

$$\int_{t_o}^{t_f} C\,dt = -\frac{C_o}{k} e^{-kt} \Bigg|_{t_o}^{t_f} \qquad [1]$$

where C_o is the initial DAC concentration, k is the first-order rate constant for DAC decomposition, $t_o = 0$, and t_i = time of exposure.

RESULTS

Growth Inhibitory Effects of DAC on L1210 In Vitro

Results of a representative experiment demonstrating the effects of 24-hr DAC exposure on the growth of L1210 are shown in figure 1A. Following drug washout (t = o) there was a dose-dependent inhibition of growth. Concentrations of DAC < 0.5 μg/ml produced a moderate, transient slowing of cell growth. For concentrations of ⩾ 0.5 μg/ml, no growth was measurable for 72–96 hrs. This cytostasis was followed by a growth rate approximating that of untreated cells. The time required for growth to return to measurable control levels was dose-dependent over the entire range tested. Increasing the duration of exposure to DAC to 48–96 hrs produced growth inhibition similar to that obtained at 24 hrs, whereas decreasing the duration of exposure to DAC to 8 hrs produced a transient slowing of cell growth, but no complete inhibition at any concentration tested (fig 1B).

Cytotoxicity of DAC on L1210 In Vitro

In figure 2, the data illustrate that at each exposure time, clonogenicity decreases with increase in DAC concentration between 0.01 and 0.5 μg/ml. For most exposure times there is a leveling off for concentrations > 0.5 μg/ml. When cells were exposed for longer periods of 72–120 hrs, clonogenicity did not consistently decrease beyond 3 logs and a variability began to appear which was not apparent at the shorter times of exposure (fig 3). For concentrations at ⩽ 0.5 μg/ml, a maximum reduction in clonogenicity is achieved at 17–24 hrs of exposure, with longer exposures producing no additional cell kill. Exposure to DAC at 1–100 μg/ml for 120 hrs appears to be somewhat more toxic.

Because DAC spontaneously degrades in growth medium, we compared clonogenic cytotoxicity with the C × t of DAC by using equation [1] with $k = 0.0456\ hr^{-1}$ (half-life = 15.2 hrs). In medium containing L1210 cells at 37°C, DAC concentrations decline to 11.2% of the initial value by 48 hrs and to 0.42% at 120 hrs. Since the data in figure 2 illustrate that cytotoxicity is diminished as C × t is decreased, loss of drug with time is responsible for the lack of further increase in cytotoxicity with increase in exposure time at the lower starting concentrations. This process results in the time-dependent plateaus observed in figure 3. However, at the 100-μg/ml initial concentration, drug decay cannot explain the observed plateau since DAC remains at cytotoxic levels (> 0.4 μg/ml) for 120 hrs. When cells were resuspended every 24 hrs in fresh medium containing freshly dissolved DAC at 100 μg/ml, additional cell kill (0.5–1 log) was seen when compared to parallel cell suspensions in which the medium and drug were not replenished.

Effects of Incubation of DAC-Exposed Cells in Drug-Free Medium Prior to Cloning

Following incubation with DAC for 24 hrs when cytostasis appeared complete (fig 1A), cells were washed free of drug and resuspended in fresh medium. Aliquots of these treated cells were removed every 24 hrs for up to 120 hrs and their clonogenicity was determined. The results with three representative DAC concentrations are shown in figure 4. At the time of drug washout, cell clonogenicity was decreased: 0.05 μg/ml gave 1½-log decrease, and 0.5 or 10 μg/ml gave about 3½-log decrease. When these cells were then incubated in drug-free medium, subsequent clonogenicity increased with the time spent in the drug-free medium. During this period, total population cell growth was stable or barely discernible as shown in figure 1A. It is evident that cell clonogenicity increased at a time when total population growth was below the limit of detection. Since L1210 cell clonogenicity at the time of DAC washout (0.5–10 μg/ml) was < 1 in 10^3 cells, a few doublings of this viable population would give a number within the standard deviation of the total cell count. This suggests that the apparent lag in growth following DAC exposure (fig 1A) results from the presence of a large background of nondividing

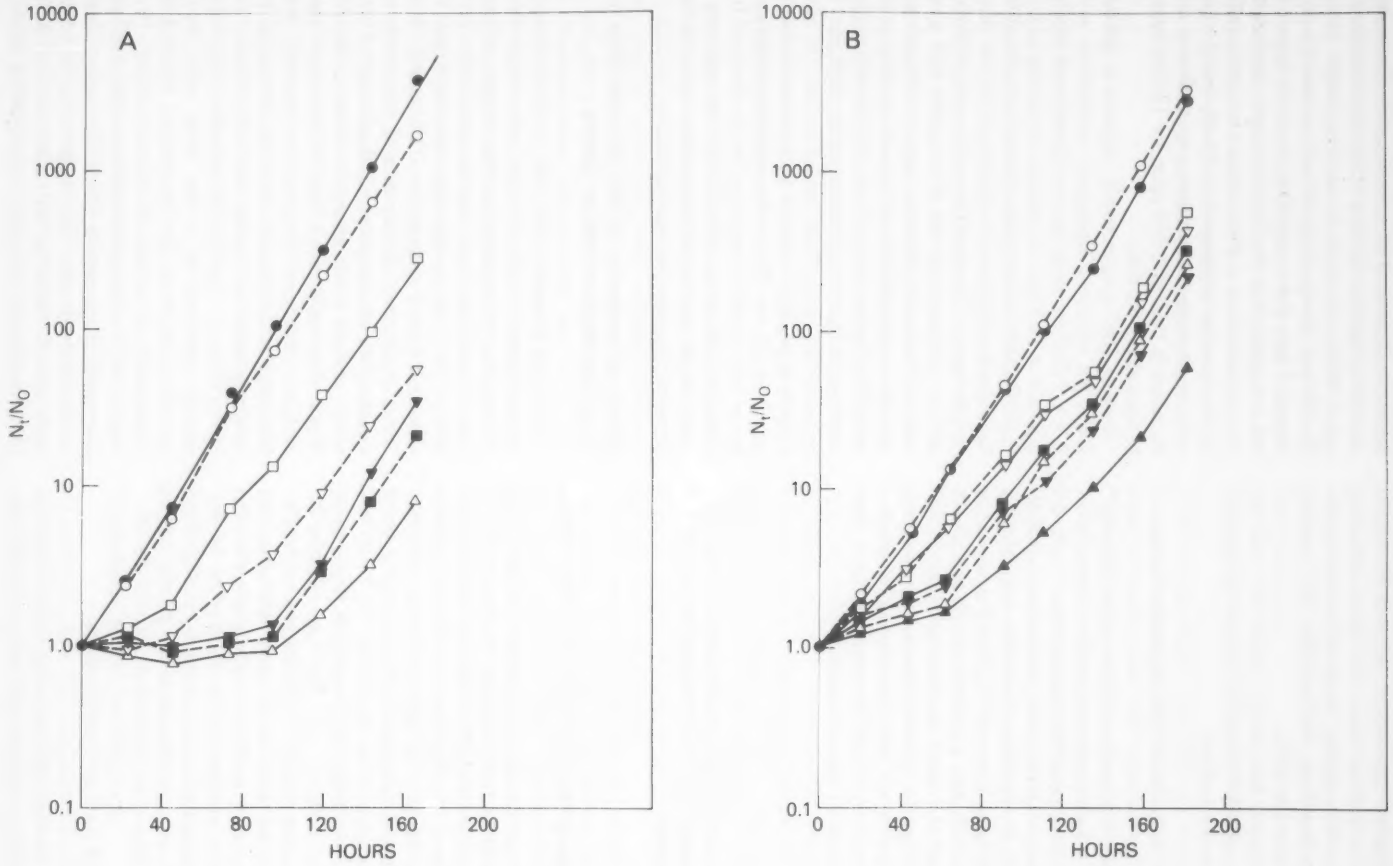

FIGURE 1.—Effects of DAC on growth of L1210 cells in vitro. Suspensions of cells were exposed to various concentrations of DAC (● = control; ○ = 0.001 μg/ml; □ = 0.05 μg/ml; ▽ = 0.01 μg/ml; ▼ = 0.50 μg/ml; ■ = 1.0 μg/ml; △ = 10 μg/ml; ▲ = 100 μg/ml) for 24 (Panel A) or 8 (Panel B) hrs. Cells were then washed and resuspended in drug-free medium. Cell Nos. at the time of drug washout (N_o) and at intervals thereafter (N_t) were determined using a Coulter Counter. N_t/N_o was plotted as a function of time following drug removal.

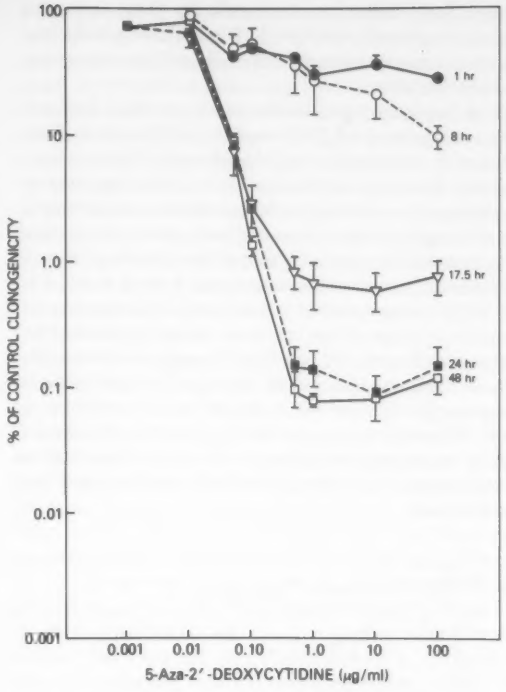

FIGURE 2.—Effect of DAC concentration on L1210 cell clonogenicity in vitro. Suspensions of cells were exposed to various concentrations of DAC for 1 hr (●), 8 hrs (○), 17.5 hrs (▽), 24 hrs (■), or 48 hrs (□). Cells were then washed, diluted, and resuspended in tubes containing fresh medium + 0.1% agar. After 13–17 days' incubation at 37°C, colonies in each tube were counted and L1210 cell clonogenicity is expressed as a % of control cloning efficiency. Each point represents the mean ± SEM of 2–6 determinations.

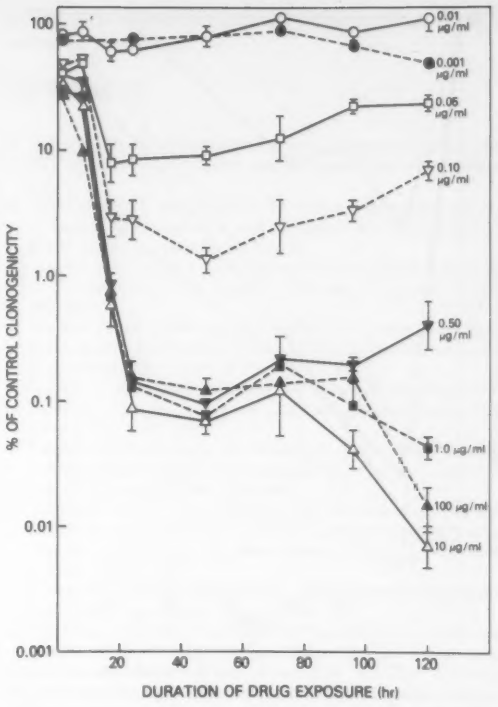

FIGURE 3.—Effect of exposure time of DAC on cloning efficiency of L1210 cells in vitro. Suspensions of cells were exposed to various concentrations of DAC (○ = 0.001 μg/ml; ● = 0.01 μg/ml; □ = 0.05 μg/ml; ▽ = 0.10 μg/ml; ▼ = 0.50 μg/ml; ■ = 1.0 μg/ml; △ = 10 μg/ml; ▲ = 100 μg/ml) for 1–120 hrs. Cells were then treated as described in the legend to fig 2 and clonogenicity was plotted as a function of exposure time to DAC prior to cloning. Each point represents the mean ± SEM of 2–6 determinations.

cells (nonclonogenic but Coulter Counter-positive), which obscure the growth of a small percentage of dividing (clonogenic) cells within the population. Those cells that escape the cytotoxic action of DAC over a 24-hr exposure period appear to be able to divide soon after their removal from the drug medium at a rate similar to that of control L1210 cells.

Cytotoxicity of Partially Degraded DAC Solutions

The cytotoxicity of freshly prepared and 8-day-old (stored at 37°C) DAC solutions is compared in figure 5. Following a 17.5-hr exposure, freshly prepared DAC produced the expected dose-response curve seen previously in figure 2 (dark circles). The 8-day-old drug produced a curve shifted to the right (dark squares), indicating a decreased cytotoxic potency of DAC after storage at 37°C. When the actual DAC concentrations of the stored solutions were determined by HPLC and the data replotted (light circles), the resultant curve was indistinguishable from that produced by fresh drug. These results suggest that the compounds produced by spontaneous degradation of DAC are not cytotoxic to L1210 and do not interfere with the cell killing actions of the parent compound.

DISCUSSION

Our data are comparable to those reported for L1210 by Momparler and Gonzales (2). Although their experiments were limited to 8-hr exposures, these investigations demonstrated 50% L1210 cell kill at 0.01 μg/ml of DAC and 90% L1210 cell kill at 0.2 μg/ml in vitro. We have found that a substantially larger L1210 cell kill (an additional 2–3 logs) can be achieved when exposures are extended beyond 8 hrs. We also observed that cytotoxicity against L1210 cells plateaus with increasing concentration at a fixed time of exposure (fig 2). This is expected for an S-phase-specific drug (1,2), since at a given exposure time, there will be a finite percentage of cells which do not enter the sensitive S phase and are thus re-

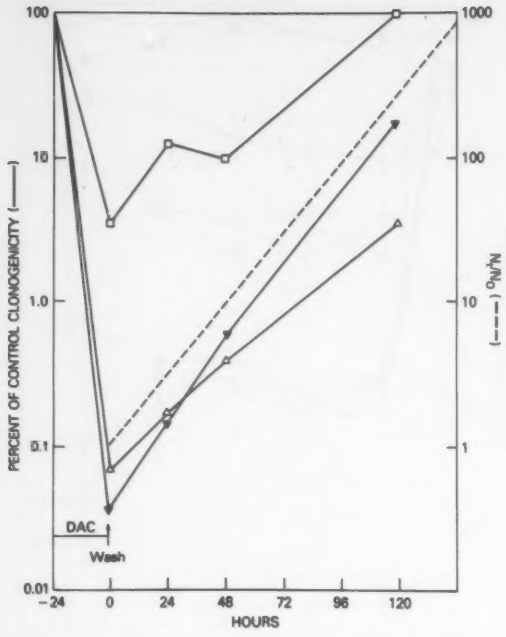

FIGURE 4.—Effect of incubation in drug-free media prior to cloning. L1210 cells were incubated in media containing 0.05 μg/ml (□), 0.50 μg/ml (▼), or 10 μg/ml (△) of DAC for 24 hrs. Cells were then washed and resuspended in drug-free media. Clonogenicity was determined by colony-formation assay immediately following drug washout and at 24, 48, and 120 hrs thereafter (solid lines). Growth of untreated cells in suspension culture was measured using a Coulter Counter and plotted as the ratio of cell No. at time = t to cell No. at t = o hr (N_t/N_o, dotted line). Clonogenicity data are from a representative experiment; the growth curve represents the mean of 15 determinations.

sistant to all concentrations of the drug. However, increasing the exposure time should result in additional cell kill. We found this to occur up to 24-hr exposure, beyond which the cytotoxicity curves leveled off with increases in exposure time (fig 3). One explanation for this observed plateau is related to the chemical instability of DAC. Since DAC breakdown products are apparently not cytotoxic (fig 5), degradation of parent drug does limit cell kill during long exposures at the lower initial concentrations of DAC. However, when the initial DAC concentration is 100 μg/ml, cytotoxic levels persist for up to 120 hrs and therefore refractoriness due to drug degradation is an unlikely explanation. No evidence for self-limiting actions of DAC exists (1,2). Alternatively, some L1210 cells may be biochemically resistant to DAC (for example, lacking deoxycytidine kinase). However, cytotoxicity curves obtained using cell lines cloned from single colonies which grew following high-dose/long-exposure treatment were identical to those obtained with the parent line, indicating that cells in these surviving colonies remained sensitive to DAC. These results suggest biochemical resistance either did not occur or was an unstable mutation.

Drug replenishment studies have provided evidence that resuspension of DAC-treated L1210 cells in fresh medium is a critical factor in producing additional cytotoxicity. The observed increase in cell kill with drug replenishment cannot be due to the addition of more DAC (at 100 μg/ml initial concentration), since the original drug remains at maximal cytotoxic levels during the period studied. These results suggest that a small fraction of the L1210 cell population is prevented from entering the sensitive S phase of the cell cycle during cytotoxic DAC exposures of up to 120 hrs. Centrifugation and resuspension in fresh medium allow these DAC-treated cells to progress through the cell cycle and become sensitive to DAC. This effect may be related to nutrient depletion and/or waste product buildup in the media. Experiments are in progress to further elucidate the mechanism of this phenomenon.

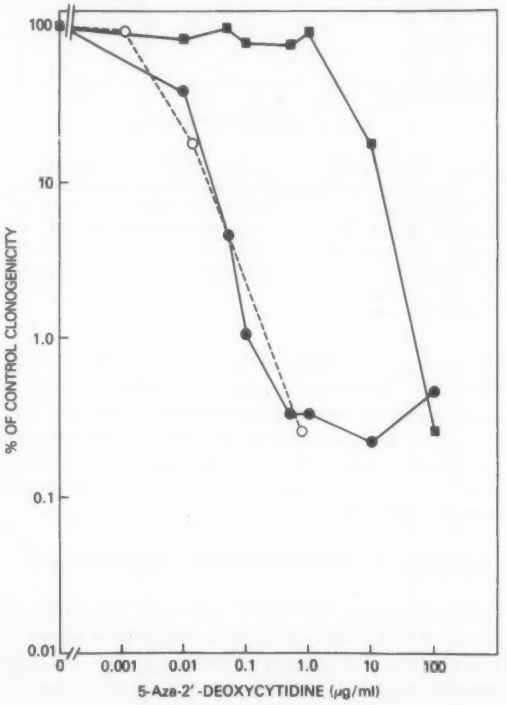

FIGURE 5.—Comparison of the cytotoxicity of freshly prepared with 8-day-old DAC solutions. ● = DAC solutions prepared and added to cells within 15 mins; ■ = DAC solutions stored for 8 days at 37°C before use; ○ = data for stored solutions corrected to indicate actual DAC concentrations as determined by HPLC.

One purpose of these studies was to relate in vitro cytotoxicity data to potential in vivo treatment schedules. Our results indicate that L1210 cell kill may be maximized by schedules producing DAC concentrations between 0.5 and 1.0 μg/ml for 24-48 hrs (figs 2 and 3). Exposure beyond 48 hrs may provide additional cytotoxicity if spontaneous drug degradation is prevented. While direct extrapolation of in vitro results to in vivo treatments cannot take into consideration animal host factors (drug toxicity to critical normal tissues, immunological effects, drug metabolism and distribution, anatomical sanctuaries for tumor, or differences between the in vivo and in vitro microenvironment), it provides a starting point for future in vivo studies.

There is a discrepancy between in vitro and in vivo estimates of DAC cytotoxicity. The maximum cell kill we observed in vitro was 3-5 logs. In contrast, Momparler and Gonzales (2) reported up to 12 logs of cell kill in vivo, and single-dose and infusion studies in our laboratory (11,12) have produced cytotoxicity estimates of 6-7 logs. There are several possible explanations for these observations. Since in vivo estimates of cell kill are based on linear extrapolations of total-body burden of tumor cells, according to the methods of Skipper et al (10), a change in the growth rate of cells surviving drug treatment will induce an overestimation of cell kill. Our studies have demonstrated that there may be a slight decrease in the growth rate of clonogenic cells following exposure to DAC in vitro (fig 4). Even a relatively small change in doubling time can lead to large overestimates of cell kill in vivo. Alternatively, it is possible that some of the higher cell kills obtained in vivo are indeed valid and result from effects of DAC modulation of the host immune system, a process which would not be observed in vitro. Further studies will be required to substantiate this hypothesis, but since DAC has been shown to have effects on the control of gene expression and cell differentiation (7-9), it remains a possibility.

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Antileukemic Activity of 5-Aza-2′-deoxycytidine and Cytarabine Against Intracerebral L1210 Murine Leukemia[1,2]

Guy G. Chabot[3,4] and Richard L. Momparler[3,5,*]

The effect of different doses of 5-aza-2′-deoxycytidine (5-aza-dCyd) or cytarabine (ara-C) on the survival time of mice with intracerebral (ic) L1210 leukemia was compared. $CD2F_1$ mice were given ic inoculation of 10^3 L1210 cells, and chemotherapy was given as a 12-hour iv infusion at various days thereafter. Treatment on Day 6 with increasing doses of 5-aza-dCyd reached a mean maximal percent increase in lifespan (ILS) of 118% at 20 mg/kg, whereas the mean maximal ILS reached for ara-C was about 60% at 1000 mg/kg. When these equitoxic doses of each drug, as determined by body weight loss, were given on Day 3, 4, or 5, 5-aza-dCyd gave greater ILS and more 60-day survivors than ara-C. These data indicate that 5-aza-dCyd is more effective than ara-C against the ic L1210 leukemia. [Cancer Treat Rep 68:1483–1487, 1984]

One of the major reasons for failure in the chemotherapy of leukemia is the presence of leukemic cells in anatomical sanctuaries such as the cerebrospinal fluid (CSF). This condition is related to the inability of most antileukemic drugs to attain cytotoxic concentrations in the CSF when given iv. The deoxycytidine analog 5-aza-2′-deoxycytidine (5-aza-dCyd), a new antileukemic agent undergoing clinical trial at this institution (1), was shown to cross the blood-CSF barrier in rabbits, dogs, and humans (2).

In this report, we have evaluated the therapeutic ability of 5-aza-dCyd against intracerebral (ic) L1210 murine leukemia. We also compared the efficacy of 5-aza-dCyd to that of cytarabine (ara-C), another deoxycytidine analog which can enter the CSF (3) and produce a potent antineoplastic effect in mice with ic L1210 leukemia (4,5). We observed that 5-aza-dCyd can prolong life significantly and even cure mice bearing the ic L1210 leukemia. Using equitoxic doses, as determined by body weight loss, 5-aza-dCyd was also shown to be more effective in this model than ara-C. A preliminary report of this work has been presented (6).

MATERIALS AND METHODS

Drugs.—5-Aza-dCyd and ara-C were obtained from Chemapol (Prague, Czechoslovakia) and the Division of Cancer Treatment (National Cancer Institute, Bethesda, MD), respectively. Drugs were dissolved in 0.9% NaCl solution containing 10 mM phosphate buffer, pH 6.8, and were filtered through a 0.2-μm filter.

Pharmacokinetic studies.—5-Aza-dCyd was administered to male $CD2F_1$ mice (BALB/c × DBA/2), 30–33 g, at a dose of 2.5 mg/kg in a volume of 0.1 ml by the iv, ip, or oral route. Mice were killed by cervical dislocation at various times thereafter, and blood was obtained by cardiac puncture using a heparinized tuberculin syringe. The drug concentration in plasma was determined by an in vitro growth inhibition assay using the L1210 leukemic cells as previously described (2). The concentration-time data were analyzed using NONLIN, a nonlinear regression program (7). Elimination kinetics was assumed to be first-order and a weighting factor of the reciprocal concentration was used.

Ic L1210 cell inoculation.—L1210 leukemic cells were maintained in $CD2F_1$ mice by weekly ip injections of 10^4 cells suspended in 0.1 ml of minimal essential medium. L1210 cells were counted using a hemocytometer, and a suspension containing 10^3 cells/0.05 ml was prepared. Under a light ether anesthesia, 0.05 ml was slowly injected by the ic route, midway between the orbit and the ear, using a tuberculin syringe equipped with a 27-gauge

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[5]We thank Louise F. Momparler for assistance in this work.

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(½ inch) needle. A plastic stopper was placed at 2.5 mm from the needle tip. For the characterization of the model, a standard survival curve was done injecting different numbers of L1210 cells ranging from 10^1 to 10^5 cells, and the survival time was recorded twice a day. At least three mice were used per group for this experiment.

Chemotherapy.—The chemotherapy was administered on Day 3, 4, 5, or 6 after the ic injection of 10^3 L1210 leukemic cells. The drugs were given to mice as a 12-hour iv infusion via a tail vein, using a Harvard pump at a flow rate of 0.25 ml/hour as previously described (8).

Endpoints for assessing chemotherapy.—The animals were checked daily for survival. The percent increase in lifespan (ILS), excluding the 60-day survivors, was calculated as follows: ((mean day of death of treated mice − mean day of death of controls)/mean day of death of controls) × 100. The toxicity was assessed by weighing the mice 7 days after chemotherapy, which corresponded to the nadir of the body weight loss. The 60-day survivors were considered cured.

RESULTS

The 5-aza-dCyd plasma concentrations versus time after the administration of 2.5 mg/kg of 5-aza-dCyd to mice, using iv, ip, or oral routes, are shown in figure 1. The plasma half-lives were independent of the route of administration and were in the range of 25–29 minutes (table 1). The areas under the curves (AUC) after the ip or oral route were 41% and 9%, respectively, of the AUC after the iv administration. Due to this limited systemic bioavailability observed with ip or oral routes, the iv route was used for the following chemotherapeutic studies.

The characterization of the ic L1210 leukemia model gave a linear relationship between the logarithm of the number of cells injected and the survival time of the animals. A linear regression analysis of this curve yielded the following equation: $y = -1.36 \log x + 15$ ($r^2 = 0.95$), where y is the survival time in days and x is the number of L1210 cells injected. The in vivo doubling time of the L1210 cells calculated from the slope of this curve was 12.2 hours. The survival times after injection of 10^2 or 10^5 cells were 12.3 and 8.2 days, respectively (data not shown).

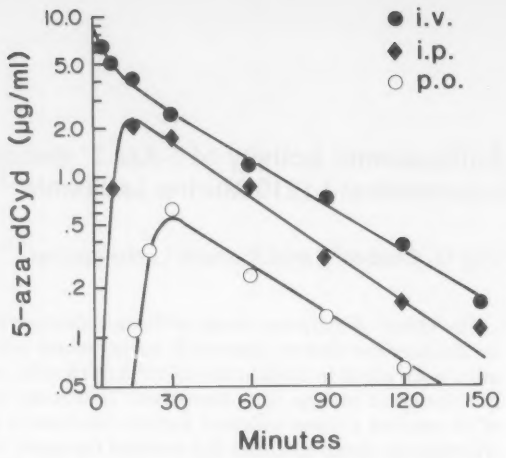

FIGURE 1.—Plasma concentrations of 5-aza-dCyd in mice after the administration of 2.5 mg/kg via the iv, ip, and oral (po) routes. Each point represents the 5-aza-dCyd concentration of the pooled plasma of 3 mice as determined by bioassay. The solid lines are the computer-generated best fit curves.

The effect of the administration of different doses of 5-aza-dCyd or ara-C, 6 days after the ic inoculation of 10^3 L1210 cells, is shown in table 2. The mean survival time of untreated mice was 10.9 days. The ILS increased with the dose of 5-aza-dCyd up to 20 mg/kg. Beyond this dose, no further increase in ILS was noted. The maximum mean ILS for the higher doses (20–67 mg/kg) of 5-aza-dCyd was 118%. For ara-C, the dose giving the optimal antileukemic effect was about 1000 mg/kg. The higher doses (1000–3400 mg/kg) of ara-C gave a mean ILS of 60%, which is about one-half of the maximal ILS noted with 5-aza-dCyd. The marked decreases in body weights probably reflected the effects of both drug toxicity and advanced leukemic disease. The estimated leukemic cell burden at the beginning of chemotherapy was about 4×10^6 cells.

The doses of 20 mg/kg for 5-aza-dCyd and 1000 mg/kg

TABLE 1.—Pharmacokinetic parameters of 5-aza-dCyd in the mouse*

Route of administration	Plasma half-life (mins)	Absorption constant (min^{-1})	Apparent volume of distribution (ml/kg)	AUC† (µg/ml) × mins	F‡ (%)
Iv bolus	29		451	242	100
Ip	27	0.27	394	100	41
Oral	25	0.12	369	21	9

*$CD2F_1$ mice were given 2.5 mg/kg of 5-aza-dCyd via the indicated routes, and blood samples were taken at various times thereafter. The concentrations were determined by bioassay.

†Area under the curve from time 0 to infinity.

‡Fraction of the dose reaching the circulation, considering the iv route as 100%.

for ara-C were chosen for the next experiments, because these doses gave the maximum antileukemic effect with approximately the same toxicity, as determined by body weight loss. At these doses, the calculated steady-state plasma concentrations, based on pharmacokinetic parameters, were about 2.5 and 125 μg/ml for 5-aza-dCyd and ara-C, respectively. The effect of these doses of each drug administered 3, 4, or 5 days after the ic L1210 inoculation of 10^3 cells is shown in table 3. In this series of experiments, 5-aza-dCyd gave greater ILS values for each day of treatment than did ara-C. Moreover, 5-aza-dCyd gave more 60-day long-term survivors than did ara-C. The total number of "cures" was 15 for 5-aza-dCyd and seven for ara-C. At these doses, the toxicity of both drugs was similar, as determined by the percent body weight loss 7 days after chemotherapy.

DISCUSSION

5-Aza-dCyd is a very interesting antileukemic agent with demonstrated efficacy in animal models (8,9) and in humans (1). Its ability to reach cytotoxic concentrations in the CSF of different species, including man (1,2), is a major asset for this drug, since meningeal leukemia is still a serious problem in the treatment of leukemias. In this report, we have evaluated the efficacy of 5-aza-dCyd against the L1210 ic murine leukemia. This model was chosen because of the similar pathology with the human meningeal leukemia (10). 5-Aza-dCyd was also compared to ara-C, another deoxycytidine analog possessing antileukemic properties with demonstrated ability to cross the blood-CSF barrier (3–5).

The iv infusion mode was chosen because of the limited systemic bioavailability of 5-aza-dCyd when given ip or orally, which suggests that this drug is rapidly metabolized by hepatic cytidine deaminase, since this drug was shown to be an active substrate for this enzyme (11). The very low bioavailability of 5-aza-dCyd via the oral route (9%) compared to the ip route (41%) is probably due to the chemical decomposition of this drug in gastric acid medium, since this drug is unstable at low pH (12); also, its enzymatic degradation by the cytidine deaminase present in the gastrointestinal mucosa may occur (13). The iv infusion was given over 12 hours to permit all of the leukemic L1210 cells to enter the DNA synthetic phase, because 5-aza-dCyd (14) and ara-C are both S-phase-specific agents and the cell cycle of L1210 leukemic cells is about 12 hours (5). This mode of administration also allows the maintenance of a steady plasma concentration, thus avoiding possible escape of leukemic cells from cell killing which could occur if the drug was given as an iv bolus.

The greater efficacy of 5-aza-dCyd as compared to ara-C against the ic L1210 leukemia when equitoxic doses are used is difficult to explain in terms of the pharmacokinetics of each agent. In fact, these two drugs diffuse into the CSF to a similar extent (2,3), and the half-life of both agents is comparable in mice (table 1) (5). Thus, neither drug seems to present a pharmacokinetic advantage over the other.

A difference in the affinity of these drugs for the catalytic site of deoxycytidine kinase could explain their difference in therapeutic efficacy, since both agents need to be first phosphorylated to be active. In fact, the Km of 5-aza-dCyd for deoxycytidine kinase (15) is greater than the Km of ara-C for the same enzyme (16), suggesting

TABLE 2.—Effect of different doses of 5-aza-dCyd or ara-C on the survival time of mice with ic L1210 leukemia*

Drug	Dose (mg/kg)	Mean survival time (days ± SD)	ILS (%)	Body weight loss† (%)
5-Aza-dCyd	0	10.7 ± 0.6	0	
	1	11.1 ± 0.4	4	
	5	15.2 ± 1.7	43	-35‡
	20	23.8 ± 3.9	122	-20
	30	22.8 ± 4.5	113	-24
	45	23.0 ± 4.5	115	-24
	67	23.6 ± 3.8	121	-28
Ara-C	0	11.2 ± 0.4	0	
	48	14.5 ± 2.4	30	
	231	14.0 ± 2.2	25	-19‡
	1000	17.6 ± 0.6	57	-18
	1500	17.2 ± 1.3	54	-17
	2300	19.4 ± 4.7	73	-20
	3400	17.6 ± 1.7	57	-18

* On Day 0, 10^3 leukemic cells were injected ic, and on Day 6, the chemotherapy was administered at the indicated total dose as a 12-hr iv infusion. There were 5 mice/group.

†Body weight loss as determined 7 days after chemotherapy.

‡These means contain dying animals, and the body weight loss is in large part due to the advanced leukemia itself. In the case of ara-C, only 3 of 5 animals were weighed.

TABLE 3.—Effect of equitoxic doses of 5-aza-dCyd and ara-C administered on Day 3, 4, or 5 on the survival time of mice with ic L1210 leukemia*

Drug (dose)	Day of treatment	Mean survival time (days ± SD)	ILS (%)	60-day survivors	Body weight loss† (%)
None		11.8 ± 0.9			
5-Aza-dCyd (20 mg/kg)	3	29.0	146	9/10	-10.7
	4	25.5 ± 5.5	116	4/10	-9.7
	5	28.8 ± 9.1	144	2/10	-13.1
Ara-C (1000 mg/kg)	3	26.8 ± 8.2	127	5/9	-12.0
	4	21.2 ± 6.9	80	2/10	-12.6
	5	20.0 ± 1.8	69	0/10	-12.4

*On Day 0, 10^3 L1210 leukemic cells were injected ic, and on Day 3, 4, or 5, the chemotherapy was administered at the indicated dose as a 12-hr iv infusion. 2 separate experiments using 5 mice/group each gave similar results.
†Body weight loss as determined 7 days after chemotherapy.

that ara-C is phosphorylated more rapidly than 5-aza-dCyd. Consequently, the greater efficacy of 5-aza-dCyd over ara-C is probably not due to a different affinity for deoxycytidine kinase.

Although 5-aza-dCyd and ara-C are both deoxycytidine analogs, they are different in many aspects, which could explain some of the differences in their chemotherapeutic activity. First, 5-aza-dCyd is extensively incorporated into DNA (17), whereas ara-C is incorporated to a limited extent because of its inhibitory effect on DNA synthesis (18). Second, 5-aza-dCyd is not as good a substrate as ara-C for cytidine deaminase (11), which could give the former drug an advantage in vivo. Third, 5-aza-dCyd can induce differentiation of many cell lines, presumably because of its inhibition of DNA methylation (19). Furthermore, the antileukemic activity of this drug in the L1210 model was also correlated with hypomethylation of DNA (20). Fourth, ara-C can block the progression of cells at the G_1-S border (21), whereas 5-aza-dCyd does not impede the progression of L1210 leukemic cells through the S phase (22) where its cytotoxic action is maximal. Thus, it is possible that part of the cytotoxic action of ara-C might be self-limiting, but not for 5-aza-dCyd.

5-Aza-dCyd was shown to significantly increase the lifespan and even cure mice bearing the ic L1210 leukemia. These observations confirmed the ability of 5-aza-dCyd to reach cytotoxic concentrations in the CSF (2), even in the presence of meningeal leukemia. Moreover, 5-aza-dCyd was also shown to be more effective in this model than ara-C when equitoxic doses, as determined by body weight loss, were used. Because of its interesting antileukemic properties and its penetration into the CSF, 5-aza-dCyd merits further investigation in the therapy of human leukemia.

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Use of Decline in D-Xylose Absorption To Predict Infection Following Intensive Chemotherapy[1,2,3]

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Oral D-xylose absorption and urinary excretion were measured before and after 32 courses of intensive chemotherapy in 14 patients with acute leukemia in complete remission. The incidence of severe and life-threatening infectious complications was greatest in those patients in whom the absorption and excretion of D-xylose fell below normal immediately following 4–7 days of chemotherapy. Gram-negative bacilli and staphylococci were the most common organisms to cause bacteremia in these patients. [Cancer Treat Rep 68:1489–1491, 1984]

Cytotoxic chemotherapy for acute leukemia causes myelosuppression and neutropenia and may also injure the intestinal mucosa, leading to an increased risk of transmural infection as well as malabsorption of nutrients and drugs (1). Since the rate of absorption and subsequent urinary excretion of the pentose sugar D-xylose depends primarily on the functional integrity of the jejunal mucosa, we used the change in D-xylose excretion (DXE) following a course of chemotherapy as a measure of the severity of gut injury (2–4). Our hypothesis was that decreased DXE would identify a patient with bowel toxicity who would thus be more susceptible to infectious complications. Our data suggest that among patients with an initially normal gut epithelium (normal DXE), a subpopulation can be identified at the conclusion of each chemotherapy treatment who may be at increased risk of infection from endogenous bacterial flora during the subsequent period of leukopenia.

PATIENTS AND METHODS

Fourteen patients with acute nonlymphocytic leukemia in complete remission were studied at the University of Chicago Clinical Research Center while receiving one to four courses of remission consolidation chemotherapy. All patients were asymptomatic, ambulatory, and eating a normal diet prior to each course of therapy. Four intensive chemotherapy regimens using cytarabine and doxorubicin or amsacrine and designed to induce marrow hypoplasia were used. All chemotherapy was given in hospital over either 4 or 7 days. All patients received prophylactic oral cotrimoxazole and nystatin from the first day of chemotherapy until the peripheral wbc count recovered to $> 1000/\mu l$. Compliance was > 80%.

DXE tests were administered on the day preceding and at the conclusion of each 4- or 7-day course of chemotherapy. Food was withheld, but fluids were not restricted during the test. After voiding completely, patients received an oral dose of 25 g of D-xylose in 250 ml of water, followed by an additional 250 ml of water. Urine was collected for the next 5 hours, and the D-xylose content was measured by the method of Roe and Rice (3). Only patients initially excreting > 4.2 g/5 hours (two standard deviations below the mean for the normal population) were evaluated (4).

Episodes of infection following chemotherapy were defined as follows. *Mild*—fever to > 38.0°C but defervescence without parenteral antibiotics; *severe*—fever to > 38.5°C requiring rehospitalization and parenteral antibiotics; and *life-threatening*—bacteremia or pneumonia confirmed by positive cultures. Isolated positive blood cultures with organisms of low virulence (JK diphtheroids) or possible skin contaminants (*Staphylococcus epidermidis*) were scored as "severe" infections.

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RESULTS

Marked myelosuppression was produced in every patient, the wbc count falling to 100–1100/μl and the platelet count falling to 2000–34,000/μl. Patients remained leukopenic (wbc counts < 1000 cells/μl) for a median of 11 days (range, 0–29). The median lowest wbc count was 300/μl, and in most cases the absolute neutrophil count dropped to < 500/μl. All patients required multiple rbc and platelet transfusions. Neither the duration of neutropenia or of thrombocytopenia nor the number of rbc transfusions required correlated with the degree of gut mucosal injury as determined by the change in D-xylose absorption, measured before and after chemotherapy (ΔDXE = pretherapy DXE –posttherapy DXE).

Gastrointestinal symptoms during or immediately following chemotherapy were mild to moderate, and direct evidence for mucosal toxicity was rare. DXE declined in all three courses of chemotherapy complicated by oral mucositis. One of these courses was further complicated by an upper gastrointestinal hemorrhage and *Pseudomonas* sepsis (ΔDXE, -9.7 g), and a second by severe dehydrating diarrhea and *Clostridium* sepsis (ΔDXE, -2.9 g).

The mean ΔDXE (-1.9 ± 2.6 g; mean ± SD) for all 32 courses of chemotherapy was highly significant (P = 0.001; paired t test). ΔDXE ranged from -9.7 to +2.5 g; in 25 patients (Group A), the posttherapy DXE declined (median, -2.1 g); in two patients (Group B), the DXE remained unchanged; and in five patients (Group C), ΔDXE increased (median, +2.0 g). A decline in DXE was associated with an increased incidence and severity of infection (fig 1), although the coefficient of correlation was not high. Severe or life-threatening infections requiring rehospitalization and parenteral antibiotics occurred in 12 of the 25 Group A patients (48%) but in only two of the seven Group B and C patients (29%). Of those ten Group A patients whose posttherapy DXE declined below the lower limit of normal (< 4.2 g), six (60%) had severe or life-threatening infections. In addition, all seven proven bacteremias occurred in Group A patients: *Escherichia coli* (two patients), *Pseudomonas* (one), *Enterobacter* (one), *Clostridium* (one), *Streptococcus viridans* and JK diphtheroids (one), and *Staphylococcus aureus* and *Staphylococcus epidermidis* (one). The median ΔDXE = -2.9 g for this bacteremic group.

Twelve of the 14 patients were studied during two or more courses of chemotherapy. Four patients had two se-

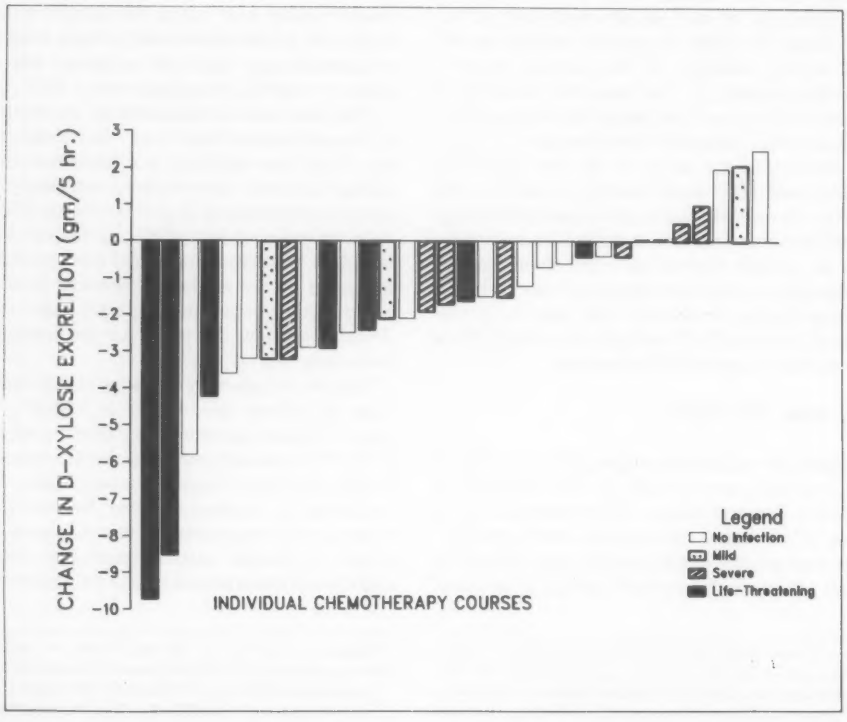

FIGURE 1.—Incidence and severity of infection following 32 courses of chemotherapy are shown for patients whose initial D-xylose absorption and excretion were normal.

vere or life-threatening infections during ten times at risk (median ΔDXE, -2.0 g); these patients had significantly more infections than expected for the group overall (χ^2, 5.6; $P < 0.05$). Six patients each had a single serious infection during 12 times at risk (median ΔDXE, -2.2 g), and four had no infections during ten times at risk (median ΔDXE, -1.2 g). No patients died. No significant differences between mean ΔDXE values were noted when the four individual chemotherapy regimens were compared, nor was there any difference when the 4-day regimen was compared to the three 7-day regimens combined.

DISCUSSION

In this study, the incidence of severe and life-threatening infectious complications was greatest in those patients in whom the absorption and excretion of D-xylose fell below normal immediately following a 4–7-day course of intensive cytotoxic chemotherapy. Since antileukemic chemotherapy drugs are cytotoxic to rapidly proliferating cell populations, the crypt portions of the intestinal mucosa and the hematopoietic tissues may be equally vulnerable. These changes are characterized by surface glandular epithelial atypia, cellular immaturity, and necrosis. Of note, the most common organisms cultured from the blood of our patients were gram-negative bacteria or *Staphylococcus* species commonly present within the intestinal lumen.

D-Xylose absorption has been found to be abnormally low in primary intestinal malabsorption states due to jejunal lesions (2,4). Therefore, we used the change in D-xylose absorption, measured prior to and immediately following a course of intensive chemotherapy, as a measure of injury to the gut epithelium. We assumed that toxicity to the colon would parallel that to the jejunum. Slavin et al (5) found that chemotherapeutic regimens containing cytarabine induced mucosal alterations along the entire gastrointestinal tract. The breakdown of mucosal barriers with the loss of mucous production and surface denudation combined with a reduction in the numbers of granulocytes within the lamina propria and the bone marrow may predispose patients to transmural infections due to endogenous gut flora (6).

Although the numbers of patients reported here are small and subject to replicate error, these results provide suggestive evidence that individual patients who experience a decline in DXE from normal levels following intensive chemotherapy may be at increased risk for severe infection with endogenous gastrointestinal flora. It may be possible to obtain greater sensitivity if the second DXE test is performed approximately 10 days after starting chemotherapy since cytotoxic effects on the gut epithelium may be maximal at that time. Combining the DXE test with other tests of mucosal integrity such as urinary excretion of ^{58}Co-labeled vitamin B_{12} after oral ingestion with intrinsic factor may improve our ability to detect subclinical toxicity throughout the gastrointestinal tract. Patients with significant gut epithelial damage might benefit from rigorous oral nonabsorbable antibiotic therapy or sterilized food. Earlier identification of this high-risk group may lead to prevention or more effective management of infections and to a better outcome.

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Immediate Termination of Intractable Vomiting Induced by Cisplatin Combination Chemotherapy Using an Intensive Five-Drug Antiemetic Regimen[1,2]

Patricia M. Plezia,[3] David S. Alberts,[3,*] John Kessler,[3] Matti S. Aapro,[3,4] Vivian Graham,[3] and Earl A. Surwit[3]

A five-drug parenteral antiemetic regimen was administered to 17 patients experiencing intractable vomiting following treatment with cisplatin-containing combination chemotherapy. The five-drug treatment consisted of metoclopramide (1 mg/kg iv), diphenhydramine (50 mg im), dexamethasone (20 mg iv), diazepam (5 mg iv), and thiethylperazine (10 mg im), given together at the initiation of the regimen and repeated on a predefined schedule. The number of emetic episodes, duration of nausea and vomiting, and adverse effects were recorded by trained observers. In addition, all patients completed standardized evaluation forms on the day after treatment. Thirteen patients (76%) remained free of vomiting and three (18%) had only one emesis after beginning the study treatment. No serious toxicity was encountered. We conclude that intractable vomiting induced by cisplatin-based combination chemotherapy can be successfully terminated with an aggressive parenteral antiemetic regimen. [Cancer Treat Rep 68:1493–1495, 1984]

Chemotherapy-induced nausea and vomiting has long been recognized as an obstacle to patient acceptance of potentially curative anticancer treatments. Only minimal relief of these dreaded symptoms has been accomplished with standard antiemetic drugs, such as the phenothiazines (1–3). Although newer pharmacologic approaches to the problem, including tetrahydrocannabinol (4,5), synthetic cannabinoids (6,7), metoclopramide (8,9), and corticosteroids (10,11), have shown increased antiemetic efficacy, it remains clear that no completely effective single-agent antiemetic regimen is currently available.

A theoretical hypothesis for the failure of single-agent regimens has recently been offered by Peroutka and Snyder (12). They have demonstrated, through neurotransmitter receptor binding studies, that effective antiemetic agents block at least one of three known neurotransmitters found within the chemoreceptor trigger zone, or vomiting center, in experimental animals. These include histamine (H_1), muscarinic cholinergic, and dopamine (D_2) receptors. Unfortunately, no single agent was found to substantially inhibit the activity of all three neurotransmitters.

Based on the hypothesis that combining antiemetic drugs with different mechanisms of action and toxic effects would improve the control of intractable nausea and vomiting, we designed an intensive five-drug parenteral antiemetic regimen for use in patients who had developed intractable vomiting following treatment with cisplatin-containing combination chemotherapy.

METHODS

All patients had histologically documented malignancies and were undergoing treatment at the University of Arizona Cancer Center. Patients receiving cisplatin-based chemotherapy regimens who were actively experiencing intractable vomiting (ie, four or more emeses within 6 hours) were eligible to receive the five-drug parenteral regimen. All patients had received single-

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TABLE 1.—Five-drug parenteral antiemetic regimen

Drug	Dose	Route	Schedule
Metoclopramide	1 mg/kg	iv	Repeated at 2, 5, and 8 hrs
Diphenhydramine	50 mg	im	q 12 hrs for 3 doses
Dexamethasone	20 mg	iv	q 4 hrs for 4 doses
Diazepam	5 mg	iv	Repeat at 4 hrs if needed
Thiethylperazine	10 mg	im	q 4 hrs as needed

agent antiemetic pretreatment. Patients were excluded from study if they were < 16 years of age or had insulin-dependent or poorly controlled diabetes, active psychosis, or severely compromised respiratory status. Written informed consent was obtained from each patient in accordance with institutional guidelines.

Treatment consisted of one dose each of metoclopramide (1 mg/kg iv), diphenhydramine (50 mg im), dexamethasone (20 mg iv), diazepam (5 mg iv), and thiethylperazine (10 mg im), given together on initiation of the regimen and repeated as outlined in table 1. The number of emetic episodes, duration of nausea and vomiting, nausea severity, and any adverse effects were recorded for each patient by trained Cancer Center personnel. All patients were observed by trained personnel in the hospital or clinic for a minimum of 3 hours after the five-drug regimen was initiated. In addition, all patients were asked to complete a standardized evaluation form on the following day.

RESULTS AND DISCUSSION

Seventeen patients, 14 females and three males, have been treated and evaluated to date. The median age of the patients was 58 years (range, 28–82). Cisplatin doses ranged from 40 to 80 mg/m^2 in these patients.

Prior to initiation of the five-drug treatment, patients had vomited an average of five times. The dura-

TABLE 2.—Results of 5-drug parenteral regimen

Patient No.	Cisplatin dose (mg/m^2)	Additional chemotherapy*	No. of vomiting episodes prior to 5-drug regimen	Duration of vomiting prior to 5-drug regimen (hrs)	No. vomiting episodes after 5-drug regimen
1	50	MOB	7	2.0	0
2	50	MOB	4	2.0	0
3	50	MMC, VCR	4	0.5	1
4	50	MMC	5	1.0	1
5	50	MOB	5	6.0	0
6	50	MMC	3†	3.0	0
7	50	MOB	4	1.0	0
8	50	MMC, VDS	4	3.0	0
9	40	CTX, DOX	5	1.0	0
10	50	CTX, DOX	5	2.0	1
11	50	CTX, DOX	5	1.0	0
12	50	MOB	6	1.0	0
13	50	MOB	5	5.0	0
14	50	MOB	6	2.5	0
15	50	DOX, VBL	6	1.0	3‡
16	50	MOB	6	6.0	0
17	80	VBL	5	1.0	0

*MOB = mitomycin, vincristine, and bleomycin; MMC = mitomycin; VCR = vincristine; VDS = vindesine; CTX = cyclophosphamide; DOX = doxorubicin; and VBL = vinblastine.

†5-drug regimen was begun after 3 emeses due to patient anxiety.

‡Vomiting recurred 4 hrs after 5-drug treatment.

tion of active vomiting prior to the study regimens ranged from 1 to 6 hours (table 2). Thirteen (76%) of the patients had no additional vomiting episodes after beginning the study treatment. An additional three patients (18%) had only one emesis after the study treatment was started. All patients reported being free of nausea following chemotherapy and free of nausea and vomiting the day after chemotherapy. Patients were asked to rank the effectiveness of the study treatment on a scale from 0 (no activity) to 5 (very effective). The average treatment score was 4.7.

Side effects associated with this five-drug regimen have been minimal. As anticipated, sleep was induced in 16 of the 17 patients (94%) for a period of 30–60 minutes. Diarrhea occurred in three patients; mild urinary retention and a mild dystonic reaction each occurred in one patient.

Each of the five drugs used in our antiemetic regimen was selected on the basis of its mechanism of action, toxicity, and reported efficacy as a single agent. Both metoclopramide and thiethylperazine are believed to act primarily at the dopamine receptors in the chemoreceptor trigger zone (1,8). Diphenhydramine is an antihistamine agent active at the H_1 receptors; it also possesses anticholinergic activity (12). Dexamethasone was chosen on the basis of our previous success with this agent (10). It has been proposed that the antiprostaglandin activity of the corticosteroids accounts for their antiemetic effects. Finally, diazepam was chosen on the basis of its antianxiety and amnesic properties, although it, too, possesses inherent antiemetic activity (13). In addition, we believed that diphenhydramine and diazepam decreased the high incidence of extrapyramidal reactions we have encountered when administering metoclopramide alone (14).

This preliminary study demonstrates our ability to terminate intractable vomiting induced by cisplatin-based combination chemotherapy with an aggressive parenteral regimen. Successful termination was accomplished in 94% of the patients. While sedation was universal, overall side effects were minimal and patient acceptance was very favorable. Based on these results, we believe that combination antiemetic therapy aimed at multiple receptor blockade may offer an important new direction toward elimination of chemotherapy-induced nausea and vomiting. The relative efficacy of the present antiemetic regimen will require additional controlled trials.

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Phase II Trial of Cisplatin in Advanced Gastric Cancer[1,2]

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Based on an initial report of activity from a small trial in Oviedo, Spain (1), the Eastern Cooperative Oncology Group (ECOG) sought to confirm that cisplatin is a useful drug in the treatment of advanced gastric cancer. The schedule for the present trial was one suited for outpatient administration and one that has demonstrated activity against non-small cell cancer of the lung (2). The program consisted of 75 mg/m^2 of cisplatin every 7 days for 3 weeks, then every 21 days. The drug was given as an iv bolus 30 minutes after an iv bolus injection of furosemide and institution of a 2-hour infusion of 2 L of 0.45% sodium chloride in 5% dextrose in water. Cisplatin was immediately preceded by a bolus injection of 12.5 g of mannitol. Doses were reduced by 50% for wbc counts of 3000-4000/μl or platelet counts of 75,000-100,000/μl; doses were withheld for blood cell counts below these limits and also for serum creatinine elevation > 150% of the pretreatment value. Treatment continued until there was evidence of disease progression.

Eligibility was restricted to patients with: (*a*) recurrent or metastatic gastric adenocarcinoma whose tumor had progressed in spite of prior chemotherapy; (*b*) measurable tumor masses; and (*c*) wbc count ≥ 4000/μl, platelet count ≥ 100,000/μl, serum creatinine ≤ 1.5 mg/dl, and performance status < 4 on the ECOG scale.

Ten patients were entered; seven were male. The median age was 56 years (range, 42-76); the median time from diagnosis was 9 months (range, 2-108). The median number of prior chemotherapy drugs was three (range, two to five), given in two regimens to five of the patients. Three patients had responded objectively to prior chemotherapy before their disease progressed. Performance status was 1 in three patients, 2 in five, and 3 in two. Seven patients had had prior gastric resections, and one had had prior irradiation. Sites of metastatic disease included: supraclavicular nodes (four patients), other nodes (two), liver (three), abdominal mass (two), skin (three), and rectal shelf (one). Five had a residual or recurrent tumor in the stomach.

Two patients had objective partial responses lasting 4 months (decrease in palpable liver edge from 10 to 2 cm below the costal margin) and 2 months (90% reduction in neck nodes and skin nodules), both measured from date of entry into study. Response was noted within 3 weeks in each case. One of the two responders had responded to prior chemotherapy. A third patient had 75% shrinkage of a supraclavicular node with only 35% shrinkage of a large abdominal mass, lasting 2.5 months; this patient did not meet strict ECOG criteria for partial remission. Among the nonresponding patients, three received only two doses, three received three doses, and one each received four and five doses of cisplatin.

Median survival was 3 months (range, 2 weeks-7 months). The two objective responders lived 5 months and 7 months from date of entry.

Moderately severe vomiting was reported in five patients, leukopenia of 2000-3000 cells/μl in three, but 1000-2000 cells/μl in only one patient. Hemoglobin < 9.5 g/dl was seen in three patients, with one requiring transfusion. Platelet counts of 50,000-75,000/μl were noted in three patients. Two patients developed transient azotemia, with peak creatinine levels of 4.2 and 2.2 mg/dl; both tolerated cisplatin given later without further renal toxicity. One patient developed late elevation in serum creatinine, not clearly attributable to cisplatin.

This trial, along with two others recently reported with responses in two of 12 and five of 14 patients (2,3), confirms the activity of cisplatin against gastric cancer in a setting of far-advanced disease in patients with a very poor prognosis. Despite an initial discouraging attempt to incorporate this drug into first-line combination chemotherapy for gastric cancer by combining it with 5-FU and doxorubicin (5), we feel further similar efforts are justified using other drugs and schedules, since cur-

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rently available programs benefit only a minority of patients, and these for only a few months (6).

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Phase II Study of Mitolactol in Chemotherapy-Refractory Metastatic Breast Cancer[1,2]

Richard H. Creech,* Robert B. Catalano, Kathleen M. Dierks, and Mukund K. Shah[3,4]

Thirty-eight evaluable patients with metastatic breast cancer refractory to hormonal therapy and multiple chemotherapy regimens were treated with mitolactol at a dose of 130 mg/m²/day orally for 10 days every 6 weeks. Only one patient, with nodal and chest wall metastases, had a sustained complete regression; two patients had stable disease; and 35 patients had disease progression. The toxicity, which was primarily hematologic, was acceptable. [Cancer Treat Rep 68:1499–1501, 1984]

In metastatic breast carcinoma, improvements in the response rates and durations of response have been accomplished by combining two or more of the following active single drugs: doxorubicin, cyclophosphamide, methotrexate, and 5-FU. Recently, mitomycin (1) and infusion vinblastine (2) have also been found to be active. In an attempt to find other effective drugs, hormonal- and chemotherapy-refractory patients were treated with mitolactol (DBD) at a dose of 130 mg/m²/day orally for 10 days at 6-week intervals.

PATIENTS AND METHODS

This phase II study of metastatic female breast cancer required patients to have measurable lesions, to have failed hormonal therapy (if appropriate) and conventional chemotherapy, to have a life expectancy > 3 months, and to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–3. Patients had to have hematocrit $\geq 27\%$, wbc count $\geq 4000/mm^3$, platelet count $\geq 100{,}000/mm^3$, BUN ≤ 25 mg/dl, total bilirubin ≤ 1.5 mg/dl, and SGOT ≤ 120 IU/L. All patients had to give informed written consent prior to participation in this study.

Patients meeting the eligibility criteria started receiving DBD at 130 mg/m²/day orally for 10 days every 6 weeks and continued receiving therapy until there was evidence of progressive disease. Objective tumor response was classified according to standard ECOG response criteria, and treatment toxicity was reported according to standard ECOG criteria by type, cause, and degree (none, mild, moderate, severe, life-threatening, or lethal) (3).

RESULTS

Of the 48 patients treated with DBD, 38 were evaluable for response and toxicity. Four patients were ineligible (two had a wbc count $< 4000/mm^3$ and two had an initial PS of 4). Six patients were not evaluable (three had incorrect drug dosages administered and three did not return for follow-up). Characteristics of the 38 evaluable patients are summarized in table 1.

In this study, only one patient responded to DBD (table 2). Two patients had stable disease and the other 35 had progressive disease. The responder had previously responded to low-dose CMF (cyclophosphamide, methotrexate, and 5-FU), doxorubicin, and mitomycin and subsequently responded to infusion vinblastine. The patient first developed a DBD-induced partial regression of nodal disease at 1 month and of chest wall recurrence at 2.5 months; she then had a complete regression of the nodes at 4 months and of the chest wall lesions at 8 months.

In this trial, the breakdown of response as related to organ site was as follows. Of 25 patients with dermal/subcutaneous disease, one achieved complete response and one had stable disease; of eight patients with nodal disease, one achieved complete response; and of six patients

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TABLE 1.—Patient characteristics

Characteristic	No. of patients	No. of responses (%)
Total evaluable	38	
Age in yrs		
Median: 60		
Range: 39-74		
Disease-free interval in mos		
Median: 14		
Range: 0-192		
Interval from metastases to DBD in mos		
Median: 31		
Range: 5-216		
Performance status		
0	0	
1	17	
2	10	
3	11	
Estrogen receptors		
Positive	13	
Negative	14	
Undetermined	11	
Previous hormone therapy	17	0 (0)
Previous chemotherapy		
Adjuvant CMF	3	
CMF	34	14 (41)
Doxorubicin	37	15 (41)
Mitomycin	37	5 (14)
Vinblastine	2	0 (0)
Razoxane	1	0 (0)

with pulmonary metastases, one had stable disease. None of the 15 patients with bony metastases, six patients with liver metastases, or one patient with intra-abdominal disease responded.

The PS 1 patients had significantly longer survival times than the PS 2 and 3 patients ($P < 0.005$) (4). The median survival times for these two groups were 17 and 4 months, respectively.

The toxicity of this dosage and schedule was acceptable and primarily hematologic (table 3). A total of 107 courses of DBD were administered to the 38 evaluable patients. Thirty-eight patients received one course; 12 received two courses; three received three courses; four received four courses; two received five courses; and one received ten courses. Although grade 1 hematologic toxicity was quite frequent, only grade ≥ 2 hematologic toxicity is reported in table 3. The only other toxic effect was mucositis in two patients. Only one patient had to have a one-third dose reduction during these 107 courses of therapy due to hematologic toxicity. No patient had gastrointestinal, pulmonary, hepatic, or renal toxic effects. There were no allergic reactions.

DISCUSSION

Several investigators have studied DBD in patients with metastatic breast cancer in phase I and II trials. Sellei et al (5) reported one response among four patients at daily oral doses of 5 mg/kg/day. Andrews et al (6) reported seven responses among 16 patients at doses ranging from 2.5 to 5 mg/kg/day orally for 14-60 days. Subsequently, Andrews et al (7), utilizing DBD orally at a dose of 3.5 mg/kg/day, reported one complete and 11 partial or mixed responses among 33 patients with metastatic breast cancer. Tormey et al (8) studied 29 patients with progressive metastatic breast cancer utilizing DBD at doses varying from 70 to > 230 mg/m^2/day for 10 days every 21-28 days. They noted increasing hematologic toxicity with increasing doses of DBD. Three patients had partial regressions at doses of 210, 233, and 280 mg/m^2/day (8). The schedule of 180 mg/m^2/day for 10 days every 4 weeks suggested by Tormey in this study has been reported in a phase II study of 45 patients with chemotherapy-refractory sarcoma. In that study, Borden et al (9) found that 42% of the patients experienced a wbc count of $< 3000/mm^3$ or a platelet count of $< 90{,}000/mm^3$. In the review of DBD by Mischler et al (10), there was a combined 26% objective response rate (33 of 140 patients) in eight published series on metastatic breast cancer.

It was our intention initially to conduct a phase II study of DBD at a dose of 180 mg/m^2 orally for 10 days every 4 weeks in patients with metastatic breast cancer who had previously failed multiple chemotherapy regimens, but who continued to have adequate bone marrow reserve and a projected survival time of at least 3 months. Initially, two patients were treated at the 180-mg/m^2/day dose. The first patient had an ECOG grade 2 rbc count and grade 3 wbc count nadir at 6 weeks, with recovery at 8 weeks. Her second course resulted in a grade 3 wbc count nadir at 6 weeks, with recovery at 9 weeks. At 6 weeks, the second patient had blood cell count nadirs as follows: grade 2 rbc count, grade 3 wbc count, and grade 3 platelet count, with recovery at 8 weeks. Because of this severe hematologic toxicity and the prolonged time needed for marrow recovery, it was elected in this study to treat these extensively previously chemotherapy-

TABLE 2.—Response to DBD

Response	No. of patients	Time to progression (mos)	Survival (mos)
Complete	1	12	35
Stable	2	4, 7	14, 16
Progression	35	—	—

TABLE 3.—Hematologic toxicity*

	Total	Grade 2			Grade 3		
		Rbcs	Wbcs	Platelets	Rbcs	Wbcs	Platelets
Course 1	38	2	6	2	0	0	0
Course 2	12	0	1	1	1	1	0

* Values = No. of patients.

treated patients with 130 mg/m²/day for 10 days at 6-week intervals.

The findings in this study are at variance with previously published results. This could be due to a greater number of prior chemotherapy regimens used as well as different drug dosages and schedules. In this study, progression on at least three chemotherapy regimens required lower than recommended initial doses and may have contributed to a lower response rate. Using the same schedule and response criteria, however, Tormey et al (8) found only a 10% response rate in metastatic breast cancer patients. The doses which were associated with these responses (210, 233, and 280 mg/m²/day) were approximately twice those used in this study (130 mg/m²/day) and greater than Tormey's recommended dose of 180 mg/m²/day.

Although one of the 38 patients in this study had a dramatic and sustained partial and then complete regression, the fact that only two other patients had stabilization of their disease suggests that the response rate to DBD using this dose and schedule in this patient population is very low.

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Intermittent Iv Homoharringtonine for the Treatment of Refractory Epithelial Carcinoma of the Ovary: A Phase II Trial[1,2,3]

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Homoharringtonine is a cephalotaxine ester derived from the plant *Cephalotaxus fortinei*-Hook-f. The drug has a marked effect on protein and DNA synthesis. L1210 cells exposed to homoharringtonine show damage in the S and G_0 phases. Also, there is a block of cell progression from G_2 into M phase and from G_1 into S phase (1).

Phase I studies demonstrated the dose-limiting toxic effects to be hypotension and myelosuppression. The hypotension was ameliorated by slowing the rate of drug administration and dividing the dose over several days. A daily dose of 5 mg/m^2 given as an intermittent injection for 5 days was considered tolerable (2). In China, the cephalotaxine esters have been used as therapy for acute nonlymphocytic leukemia (3,4).

MATERIALS AND METHODS

Seventeen patients with epithelial ovarian cancer who had failed prior chemotherapy regimens received homoharringtonine. The starting dose of homoharringtonine was 3.0-4.0 mg/m^2 for 5 days. Patients with a history of prior radiation therapy or prolonged myelosuppression from previous chemotherapy received an initial dose of 3.0 mg/m^2. The drug was administered in 1 L of 5% dextrose and 0.45% NaCl solution over 4 hours. Iv antiemetics or other potentially hypotensive agents were avoided. A dosage escalation schedule provided for additional days of administration of the drug. Patients did not receive > 4.0 mg/m^2/24-hour period. Most patients were treated as inpatients. Therapy was repeated every 21-28 days, depending on hematologic recovery. Dosage escalation was aimed at producing a granulocyte count of 1000/mm^3 or a thrombocyte count of 50,000-100,000/mm^3. Patient characteristics are listed in table 1.

RESULTS

Of 17 patients, two are inevaluable. These patients were lost to follow-up with inadequate documentation of side effects or response. The remaining 15 patients developed progressive malignancy. There were no complete or partial responders. Ten patients received 3 mg/m^2 and four were increased to 4 mg/m^2. Five patients received 4 mg/m^2 initially. No patient received 4 mg/m^2 for > 6 days.

Side effects included mild nausea and vomiting in eight patients (53%). Two patients were hospitalized for neutropenia-related infections. One patient developed a rectal fistula while neutropenic. Another patient had prolonged asymptomatic neutropenia of about 60 days' duration. A bone marrow aspiration and biopsy showed marked hypoplasia. No significant hypotension was noted in any patient. Neutropenia and thrombocytopenia were dose-limiting.

Homoharringtonine may be safely administered with this dosage schedule. However, the drug does not have significant antitumor activity against refractory epithelial ovarian cancer.

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[3]Homoharringtonine was supplied by the Division of Cancer Treatment, National Cancer Institute, Bethesda, MD.

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TABLE 1.—Patient characteristics

Characteristic	No. of patients	% of patients
Total evaluable	15	100
Median age in yrs (range): 59 (45–68)		
Performance status (Zubrod)		
0	1	7
1	9	60
2	4	26
3	1	7
Prior chemotherapy (cisplatin combinations)	13	87
Median No. of regimens: 2		
Median granulocyte count nadir in cells/mm^3 (range): 1300 (250–4600)		
Courses with nadir of—		
⩽ 1000		33
⩽ 500		27
Median platelet count nadir in cells/mm^3 (range): 123,000 (17,000–348,000)		
Courses with nadir of—		
⩽ 100,000		40
< 50,000		27

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Perioperative Carmustine Chemotherapy for Malignant Brain Tumors[1,2]

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Carmustine (BCNU) has been used in the treatment of malignant brain tumors since the early 1970s. It is still considered one of the most effective chemotherapeutic agents for treating such tumors (1). To obtain better results with BCNU treatment, a series of variations from the conventional schedule of 80 mg/m^2 iv for 3 days every 8 weeks have been tried, including: dose [high doses with bone marrow rescue (2)], administration time [a single dose of 200 mg/m^2 rather than in 3-day fractions, two cycles before surgery (3,4)], and injection site [intra-arterial (5)]. This report describes preliminary results of a pilot study where the first dose of BCNU was administered in the immediate postoperative period.

From April 1982 to June 1983, 24 nonselected patients with primary malignant glioma were entered into the study. Eligibility criteria included: age > 15 years, histology of glioblastoma or anaplastic astrocytoma, preoperative performance status ≥ 40, anticipated survival of at least 8 weeks, normal hepatic and renal functions, wbc count ≥ 4000/mm^3, platelet count ≥ 100,000/mm^3, and hematocrit ≥ 35%.

BCNU was administered iv 6-8 hours after surgery in a single dose of 220 mg/m^2 over 2 hours. Radiotherapy (45 Gy whole-brain with a boost of 15 Gy on the tumor bed delivered in 6-7 weeks with megavoltage equipment) was started within 3 weeks from surgery. BCNU was repeated every 8 weeks at the same dosage for a maximum of 2 years. Dose-reduction schedule was based on hematological toxicity.

The patients underwent computerized tomographic scan 24-48 hours and 15 days after surgery and again at the end of each cycle of chemotherapy. Patients were given the lowest amount of dexamethasone necessary to maintain stable neurologic conditions.

On December 31, 1983, 21 of the 24 patients were evaluable. Two patients were excluded for insufficient data; one patient's histopathological review showed a metastasis. Characteristics of the patients are shown in table 1.

TABLE 1.—Patient characteristics

Characteristics	No. of patients
Entered	24
Evaluable	21
Age in yrs	
Median: 53	
Range: 17-70	
Sex	
Males	13
Females	8
Histology	
Glioblastoma	15
Anaplastic astrocytoma	6
Performance status (Karnofsky)	
Preoperative	
Median: 60	
Range: 40-100	
After 1st course	
Median: 80	
Range: 40-100	
Type of surgery	
Gross total resection	6
Subtotal or partial resection	15
Biopsy	0
Tumor location	
Frontal	4
Parietal	5
Temporal	11
Occipital	1
No. of chemotherapy cycles	
Median: 5	
Range: 3-10	
No. with dose reduction: 15	

Preoperative Karnofsky performance status was < 50 in seven patients (33.3%); and six patients were < 50 years of age. The duration of follow-up from the date of surgery ranged from 7 to 21 months (median, 15). The actuarial survival rates at 12 months and 16 months from

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surgery were 71.5% and 55.6%, respectively, with a median survival time of 16.5 months (fig 1).

Toxic effects were nausea, vomiting, burning at the injection site, leukopenia, and thrombocytopenia, which did not differ from our previous experience (6). In one patient the treatment was discontinued after the sixth cycle because of severe hematologic toxicity. There have been no signs of pulmonary fibrosis related to BCNU treatment.

Some experimental data suggest that the effectiveness of BCNU administration varies in relation to the amount of time elapsed after surgery. Previous observations indicate that in the 9L tumor model a dose of BCNU given > 3 days before or after surgery is less effective than BCNU alone (7). With the same experimental model, it was subsequently shown that a marked improvement was obtained, in terms of survival time, if BCNU was administered 1 hour before or 1-12 hours after surgery (8).

Our experience from this pilot study on human malignant glial tumors provided results indicating that administration of BCNU in the immediate postoperative period may be useful in prolonging survival time. In previous trials with conventional treatment (surgery, radiotherapy, and BCNU starting 15 days after surgery) our study group obtained median survival times varying between 11.6 and 12.5 months (9).

As Tel et al (8) have emphasized, surgery causes important metabolic modifications that could facilitiate BCNU delivery, thus increasing the cell kill. Also, the cell kinetic modifications induced by surgery stimulate the passage of resting cells to a proliferating pool, making them more sensitive to chemotherapeutic agents (10).

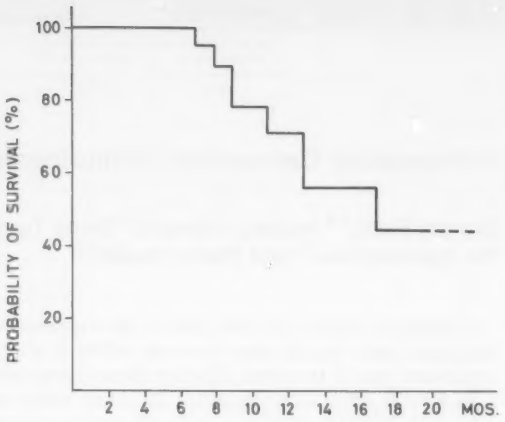

FIGURE 1.—Actuarial survival curve.

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Phase II Evaluation of 4′-Epi-doxorubicin in Patients With Metastatic Colorectal Carcinoma[1]

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4′-Epi-doxorubicin is an anthracycline antibiotic synthesized in an effort to find a compound having a therapeutic index superior to that of its parent compound, doxorubicin (1). It differs from doxorubicin only by epimerization of the hydroxyl group at the 4′ position. This reduces the affinity of the compound to DNA and results in higher intracellular levels of the active drug than those obtained with doxorubicin at equivalent doses. The antitumor activity of 4′-epi-doxorubicin is comparable to that of its parent compound when tested against Sarcoma 180 (solid and ascitic), L1210 leukemia, P388 ascitic leukemia, and 631+/He transplanted mammary carcinoma (1). In phase I studies, the side effects were similar to those of doxorubicin (2,3). However, 4′-epi-doxorubicin showed less toxicity, as suggested by the lower incidence of vomiting, stomatitis, and alopecia (2,3). Preliminary trials also suggest 4′-epi-doxorubicin to be less cardiotoxic than doxorubicin (2). We initiated a phase II evaluation of 4′-epi-doxorubicin administered every 3 weeks to patients with colorectal carcinoma.

MATERIALS AND METHODS

Patients with histologic proof of measurable metastatic colorectal carcinoma were entered in the study. All patients had been previously treated and had expected survival of > 12 weeks. Patients were required to have normal blood cell counts, normal liver function, normal renal function, and performance status of ⩽ 3 (Zubrod scale). Patients with myocardial infarction, congestive heart failure, and cardiac arrhythmias were excluded. Informed consent was obtained from all patients.

The treatment consisted of 90 mg/m^2 of 4′-epi-doxorubicin dissolved in 200 ml of 5% dextrose in water, administered iv over 30 minutes. Treatments were repeated every 3 weeks. The dose was escalated by 25% in subsequent treatments if the patient did not have thrombocytopenia (< 50,000 cells/mm^3), granulocytopenia (< 500 cells/mm^3), infection, or bleeding. Criteria for defining response were standard.

TABLE 1.—Patient characteristics and toxicity of 4′-epi-doxorubicin

Characteristics	No. of patients (%)
Total entered	41
Median age in yrs (range): 56 (36–75)	
Median performance status (range): 1 (0–3)	
Primary site	
Rectosigmoid	23
Colon (remaining)	18
Toxicity	
Hematologic [median lowest counts, × 10^3/mm^3 (range)]	
Wbc count: 2.5 (0.8–18.4)	
Granulocyte count: 1.1 (0.5–15.0)	
Platelet count: 205 (37–510)	
Nonhematologic	
Nausea and vomiting	27 (69)
Alopecia	12 (31)
Mucositis	10 (26)
Weakness	9 (23)
Fever	2 (15)
Diarrhea	3 (8)
Cardiac	3 (8)

Forty-one patients were entered. Patient characteristics and toxicity are shown in tables 1 and 2. Toxicity was defined according to National Cancer Institute criteria.[3]

RESULTS

Thirty-nine of 41 patients were evaluable for response. Two patients were lost to follow-up after one course of 4′-epi-doxorubicin. There were no partial or complete remissions. A minor tumor regression in a patient with pul-

[1]Received Oct 26, 1983; revised Mar 14, 1984; accepted June 11, 1984.

[2]Division of Medical Services, Department of Medical Oncology, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston.

[3]Investigational agent adverse drug reaction reporting chart: National Cancer Institute, Division of Cancer Treatment, Jan 1983.

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TABLE 2.—Nonhematologic toxicity, by grade

Toxic effect	Total No. of patients	No. of patients with grade—			
		1	2	3	4
Nausea and vomiting	27	13	8	4	2
Alopecia	12	2	1	1	8
Mucositis	10	5	3	2	0
Weakness	9	9	0	0	0
Fever	2	0	2	0	0
Diarrhea	3	3	0	0	0
Cardiac	3	3*	0	0	0

*Includes 1 patient with cardiomyopathy at 950 mg/m^2. Ejection fraction was normal.

monary metastasis was observed for 8 weeks, and tumor stabilization was observed in 13 (33%) patients. Median duration of stable disease was 9 weeks (range, 9–38+).

Median dose of 4′-epi-doxorubicin in all patients was 90 mg/m^2 (range, 50–1250+). Median number of courses was two (range, one to 11+), and median total dose was 180 mg/m^2 (range, 75–1250+).

One patient underwent endomyocardial biopsy at a cumulative dose of 950 mg/m^2. She had a cardiomyopathy score of 1.0, with normal ejection fraction and no clinical evidence of congestive heart failure. She continues therapy with a cumulative dose of 1250+ mg/m^2. Another patient, 72 years old, developed heart failure at 225 mg/m^2, following a gastrointestinal hemorrhage at a local hospital.

DISCUSSION

The treatment of patients with metastatic colorectal carcinoma has been frustrating. In this trial, 4′-epi-doxorubicin was given in adequate doses to 39 evaluable patients, none of whom had a complete or partial remission, indicating a lack of activity against previously treated colorectal carcinoma. Since most patients received only two courses of 4′-epi-doxorubicin, no conclusions can be drawn regarding the cardiotoxic potential of this agent.

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Phase II Trial of 4′-Epi-doxorubicin in Metastatic Melanoma[1,2]

Frank M. Torti,[3,4,5,*] Klaus J. Porzig,[6] David R. Gandara,[7] Paul Volberding,[8] Edith Mitchell,[9] Frederick J. Meyers,[10] Marsha Kohler,[5] and Melanie Gribble[5]

4′-Epi-doxorubicin is an epimer of doxorubicin in which the position of the hydroxyl group is altered at the C-4′ position of the aminosugar. In animal model systems a therapeutic index seems to be improved over that of doxorubicin: efficacy is maintained in doxorubicin-responsive tumors, while cardiac toxicity appears to be diminished (1). In phase I clinical trials in the United States and Europe, activity in tumors unresponsive to doxorubicin has also been suggested in studies with limited patient numbers. Melanoma is one such tumor type (2,3). Although limited responses have been observed in patients with melanoma treated with doxorubicin (4-6), activity has been suggested for 4′-epi-doxorubicin (2,3). Fifteen patients were entered between July 1982 and July 1983 in this Northern California Oncology Group study to evaluate the efficacy of 4′-epi-doxorubicin in melanoma.

MATERIALS AND METHODS

4′-Epi-doxorubicin was administered at 75 mg/m^2 as a slow injection over 5-10 minutes into a running iv infusion of either normal saline or dextrose in water every 3 weeks. Cycles were delayed for a wbc count < 3000/mm^3 or a platelet count < 100,000/mm^3, and doses were decreased by 25% for a wbc count of 3000-3499/mm^3 or a platelet count of 100,000-149,000/mm^3. No dose escalation was permitted. Treatment was continued until progression of disease. Only patients with measurable disease were entered.

Patient entry required adequate bone marrow, hepatic, and renal functions: creatinine < 2 mg/dl, bilirubin < 1.5 mg/dl, wbc count > 4000/mm^3, and platelet count > 100,000/mm^3. Prior extensive irradiation defined as > 4000 rads to the pelvis or mediastinum, or irradiation to > 25% of the bone marrow was allowed. Prior history of cardiac disease, including previous myocardial infarction or arrhythmias requiring medical therapy, and prior chemotherapy with doxorubicin were reasons for patient exclusion.

RESULTS

None of the 15 patients had a complete or partial response (table 1). One patient had a minor response defined as a 25%-50% reduction in tumor size. This minor response was maintained through ten cycles of chemotherapy. The median time to progression was 8 weeks and the median survival time was 20 weeks.

At the 75-mg/m^2 dose, three patients experienced hematologic toxicity: one had a nadir wbc count of 800/mm^3, one had a nadir wbc count of 2200/mm^3 (500 neutrophils) with fever and neutropenia, and one had a nadir wbc count of 2500/mm^3 with a nadir platelet count of 77,000/mm^3. These three patients had subsequent hematologic recovery and continued to receive therapy. One patient had severe nausea and vomiting. No hepatic toxicity was noted. No congestive heart failure or other clinical evidence of cardiac toxicity was noted in this trial.

DISCUSSION

4′-Epi-doxorubicin was a well-tolerated but inactive regimen in this group of patients, most of whom had had no prior chemotherapy and had a high Karnofsky performance status. In this study 4′-epi-doxorubicin had no demonstrable activity against metastatic melanoma.

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[2]Supported by Public Health Service grants CA-21744 and CA-24751 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, and by a grant from Farmitalia Carlo Erba, Milan, Italy.
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[9]David Grant Medical Center, Sacramento, CA.
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TABLE 1.—Patient characteristics and toxic effects

Characteristics	No. of patients
Total	
Entered	15
Evaluable for response and nonhematologic toxicity	15
Evaluable for hematologic toxicity	14
Median age in yrs (range): 59 (36–72)	
Sex	
Male	12
Female	3
Karnofsky performance status	
90–100	9
70–80	3
50–60	3
Prior chemotherapy	
Yes	2
No	13
Prior radiotherapy	
Extensive	1
Limited	1
None	13
Extent of disease involvement at study entry	
Local only	1
Visceral	14
No. of cycles received	
1	2
2	4
3	5
4	2
8	1
10	1
Wbc count nadir ($\times 10^3$ cells/mm^3)	
3.0–4.4	3
2.0–2.9	2
1.0–1.9	0
< 1.0	1
Complete but reversible alopecia	4*

* Occurred after receiving 4′-epi-doxorubicin at doses of 148, 219, 222, and 600 mg/m^2.

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Phase II Study of Mitoxantrone in Advanced Breast Cancer: An Eastern Cooperative Oncology Group Pilot Study[1,2]

Mark Levin,* Kishan J. Pandya, Janardan D. Khandekar, John Horton, John H. Glick, John M. Bennett, Franco M. Muggia, and Geoffrey Falkson[2,3]

Mitoxantrone is a new antitumor agent belonging to the anthraquinone class of compounds. Because of early responses seen in human breast cancer in clinical studies (1-3) and in the human tumor clonogenic assay (4), a confirmatory phase II trial was initiated by the Eastern Cooperative Oncology Group (ECOG).

MATERIALS AND METHODS

Between March 1981 and April 1983, 34 women with advanced breast cancer were treated with mitoxantrone in an ECOG pilot study. All patients had histologically documented breast adenocarcinoma with measurable metastatic disease resistant to one prior chemotherapy regimen. As recommended in phase I trials (5), mitoxantrone, 4 mg/m^2 daily × 3, was given as an iv infusion over 10 minutes in 100 ml of 5% dextrose in water every 3 weeks. A dose escalation of 20% for a wbc count nadir > 4000/mm^3 and reduction of 20% for a nadir < 2000/mm^3 were carried out. A cbc was obtained weekly; physical examination, tumor measurements, and blood chemistries were done every 3 weeks. Mandatory cardiotoxicity assessment was determined on the basis of history, physical examination, and ECG. An adequate trial of therapy consisted of one course of mitoxantrone. Patients were removed from the study when they developed progressive disease. Standard ECOG response criteria were employed (6).

RESULTS

Clinical and response data for the 34 patients are shown in table 1. Four patients had dose escalation and eight had reduction as per protocol. Neutropenia was the only hematologic toxicity. One patient developed fever requiring antibiotic therapy. One patient who had had prior radiation therapy and 400 mg/m^2 of doxorubicin developed cardiomyopathy following 122 mg/m^2 of mitoxantrone. Cardiotoxicity was also experienced by a patient treated with 480 mg/m^2 of doxorubicin after radiation therapy to the left chest wall and 26 mg/m^2 of mitoxantrone.

No complete responses were seen. Partial responses occurred in two patients (6%); the responding lesions were skin nodules in one patient and retroperitoneal lymph nodes in another, lasting 9 and 15 weeks, respectively. Neither patient had previously received doxorubicin. The response rate for the 18 patients not previously treated with doxorubicin was 11%.

DISCUSSION

The response rate of 6% obtained in these 34 patients with good performance status and only one previous chemotherapeutic treatment for metastatic disease is disappointing. Although it is in the same range of responses as the 10% seen in 110 of the Southwest Oncology Group patients and 6.5% of the Southeastern Cancer Study Group patients (2,3), it is lower than the 22% responses seen at M. D. Anderson Hospital (1). Significant neutropenia was obtained in our patients; however, the M. D. Anderson Hospital obtained wbc count nadirs < 500 in one-half of their patients prior to reducing their dose from 4 mg/m^2 to 3 mg/m^2 daily × 5 every 4 weeks (1). This variable response may indicate that mitoxantrone has a very steep dose-response curve or alternatively that dose scheduling or patient selection may be important factors for tumor response.

[1]Received Jan 24, 1984; revised May 29, 1984; accepted June 18, 1984.

[2]This study was conducted by the Eastern Cooperative Oncology Group (*Paul P. Carbone*, chairman, CA-21115) and was supported by Public Health Service grants (CA) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. The following members participated in the study: New York University Medical Center, NY (*M. Levin* and *F. M. Muggia*, CA-16395); University of Rochester Cancer Center, NY (*K. J. Pandya* and *J. M. Bennett*, CA-11083); Northwestern University Medical Center, Chicago, IL (*J. D. Khandekar*, CA-17145); Albany Medical College, NY (*J. Horton*, CA-06594); Hospital of the University of Pennsylvania, Philadelphia (*J. H. Glick*, CA-15488); and University of Pretoria, South Africa (*G. Falkson*, CA-21692).

[3]We thank Peggy Nixdorf for secretarial assistance.

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TABLE 1.—Patient characteristics

Characteristics	No. of patients
Total entered/evaluable	34/34
Median age in yrs (range): 56 (36–80)	
Performance status*	
0	6
1	21
2	7
Prior doxorubicin	
Yes	16
No	18
Prior radiation therapy	
Yes	24
No	10
Prior chemotherapy	
1 combination	27
Adjuvant + 1 combination	7
Prior hormone therapy	23
Sites of disease	
Soft tissue and bone only	14
Visceral	20
Estrogen receptor	
Positive	11
Negative	17
Unknown	6
No. of cycles of mitoxantrone therapy	
Median (range): 3 (1–15)	
Low wbc count nadir, $\times 10^3/mm^3$	
Median (range): 1.7 (0.2–4.0)	
Nausea and vomiting	
None	20
Mild	12
Severe	2
Alopecia	
Yes	5
No	29
Cardiotoxicity	
Yes	2
No	32
Response	
Complete	0
Partial	2
None	32

* Eastern Cooperative Oncology Group criteria.

In summary, mitoxantrone given at a dose of 4 mg/m^2 iv daily × 3 every 3 weeks was well tolerated but provided minimal antitumor effect in previously treated patients with advanced breast cancer.

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Phase II Trial of Etoposide in the Management of Advanced or Recurrent Non-squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study[1,2]

R. E. Slayton,[3] J. A. Blessing,[4] and H. D. Homesley[5,*]

In 1977, members of the Gynecologic Oncology Group (GOG) initiated a series of phase II trials designed to test new agents in a number of different advanced or recurrent gynecologic malignancies, including carcinoma of the cervix; they identified at least one highly active agent, cisplatin (1), and three other agents with moderate activity, dianhydrogalactitol (2), Baker's antifol (3), and razoxane (4), in squamous cell tumors of the cervix. Three agents have also been evaluated in advanced or recurrent non-squamous tumors of the cervix, with two of 14 patients exhibiting a partial response to piperazinedione and two of 13 patients showing a partial response to cisplatin (5). The results of a phase II trial of dianhydrogalactitol will be published (GOG Statistical Report, February 1984).

Etoposide was chosen for the current trial because of its activity in several nongynecologic tumors; it was given at a dose of 100 mg/m^2 diluted in 150 ml of normal saline and administered over a 45-minute period on Days 1, 3, and 5. The cycle was repeated every 28 days. A complete description of material and methods is contained in an earlier paper (6).

Complete response was defined as the disappearance of all gross evidence of disease for at least 1 month. Partial response was defined as a 50% reduction in the product of the largest diameter and its perpendicular of each measurable lesion for a period of at least 1 month. Disease progression was defined as a 50% increase in the product of the largest diameter and its perpendicular of each measurable lesion documented on two separate examinations at least 2 weeks apart, or the appearance of any new lesion within 3 months after entry in the study. Stable disease was defined as response not meeting the above criteria.

Patient characteristics, response to therapy, and adverse effects are summarized in table 1. Among 19 patients evaluated (15 with adenocarcinoma and four with adenosquamous carcinoma), only one partial response, lasting 9 months, was noted; nine patients had stable disease, while nine had increasing disease. The patient who exhibited a partial response had had previous radiation therapy to the pelvis (5500 rads) and was noted to have positive pelvic and para-aortic lymph nodes 3 months la-

TABLE 1.—Patient characteristics and results

Characteristics	No. of patients
Total evaluated	19
Age in yrs	
Median: 57	
Range: 26-84	
Performance status	
0	6
1	8
2	4
3	1
Histology	
Adenosquamous carcinoma	4
Adenocarcinoma	15
Grade	
1	4
2	5
3	10
Prior radiotherapy	15
Prior chemotherapy	5

Continued

[1]Received Mar 5, 1984; revised May 21, 1984; accepted June 8, 1984.

[2]Supported by Public Health Service grants (CA) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. The following institutions participated in the study: University of Alabama, Birmingham (CA-12482); University of Minnesota Medical School, Minneapolis (CA-23088); The Milton S. Hershey School of Medicine of Pennsylvania State University, Hershey (CA-16389); Georgetown University Hospital, Washington, DC (CA-16938); University of North Carolina School of Medicine, Chapel Hill (CA-23073); University of Texas Health Science Center at Dallas (CA-28160); Indiana University Medical Center, Indianapolis (CA-21720); Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, NC (CA-21946); Illinois Cancer Council (CA-27806); and the University of Pittsburgh School of Medicine, PA (unfunded).

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TABLE 1.—*Continued*

Characteristics	No. of patients
No. of courses	
Median: 3	
Range: 1–8	
Response	
Partial response	1
Stable disease	9
Increasing disease	9
Toxic effects	
Leukopenia	8
Thrombocytopenia	2
Anemia	2
Alopecia	3
Nausea and vomiting	3
Skin rash	1
Fatigue	1
Blurred vision	1
Elevated BUN and creatinine	1
Elevated alkaline phosphatase, SGOT	2

ter. Leukopenia was the most serious adverse effect and was observed in eight of 19 patients with a median wbc count nadir of 3150/mm^3 (range, 1600–3800). Thrombocytopenia was reported in two patients with platelet count nadirs of 109,000/mm^3 and 140,000/mm^3.

With this dose schedule, etoposide appears to be inactive in advanced or recurrent non-squamous cell carcinoma of the cervix.

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Phase II Study of Spirogermanium in Advanced Breast Cancer[1,2,3]

J. Philip Kuebler, Douglass C. Tormey,* Gregory R. Harper, Yuang-Chi Chang, Janardan D. Khandekar, and Geoffrey Falkson[3]

Spirogermanium, a heterocyclic azaspirane containing the element germanium in its structure, has a demonstrable cytotoxic effect on tumor cells in vitro (1). Although early clinical data suggested antitumor activity in breast carcinoma (2), subsequent phase II trials have yielded conflicting results (3,4). This study was designed to evaluate the activity of spirogermanium using a multiple-dose schedule shown to be optimal in phase I trial (5).

Patients with advanced, histologically documented breast cancer resistant to conventional systemic therapy were entered into the Eastern Cooperative Oncology Group (ECOG) study, provided the following criteria were met: measurable or evaluable disease; performance status ⩽ 2; no therapy within the previous 3 weeks; total wbc count ⩾ 100,000/μl; SGOT not more than two times the upper limit of normal; and informed consent. Patients with blood cell counts less than these limits or with SGOT elevations more than two times the normal were considered eligible for this study, provided the abnormal parameters were disease-related. All patients were required to have been treated with at least one, but not more than two, previous chemotherapy programs.

Patients were treated with 120 mg/m^2 of spirogermanium given as an iv infusion in 150 ml of saline over 60-90 minutes on Monday, Wednesday, and Friday of each week for a planned minimum of 8 weeks. Thereafter, one weekly infusion was given at the same dose level. Therapy was continued for at least 2 months or until disease progression occurred. Patients were evaluated weekly for response and toxicity. Neurologic toxicity in the form of somnolence, confusion, or seizures dictated a 50% dose reduction, with later escalation if tolerated during subsequent treatments. Provision was also made for slowing the infusion rate in case of central nervous system stimulation. Objective tumor responses were classified using standard ECOG criteria, except that central nervous system recurrence was not considered sufficient evidence of systemic progression.

Patient characteristics and results of therapy are presented in table 1. No objective responses were noted among the 28 eligible and seven ineligible patients in this

TABLE 1.—Patient characteristics and treatment results[*]

Characteristics	No. of patients
Age at entry (yrs)	
Mean: 59.5	
Range: 28-71	
Initial ECOG performance status†	
0	6
1	14
2	8
Estrogen receptor	
Positive	4
Negative	16
Unknown	8
Previous chemotherapy	
1 combination	13
2 combinations	15
Extent of disease	
1 disease site	8
2 disease sites	10
⩾ 3 disease sites	10
No. of dominant disease sites	
Visceral: 31	
Osseous: 15	
Soft tissue: 28	
Treatment	
Median duration, wks: 3.5	
No. completing 8 wks of therapy	4
Total dose, mg	
Mean: 1926	
Range: 152-5400	

Continued

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[2]Spirogermanium (Spiro-32) was supplied by Dr. M. G. Mulinos of Unimed, Inc, Somerville, NJ.

[3]This study was conducted by the Eastern Cooperative Oncology Group (*Paul P. Carbone*, chairman, CA-21115) and was supported by Public Health Service grants (CA) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. The following members participated in the study: Wisconsin Clinical Cancer Center, Madison (*J. P. Kuebler* and *D. C. Tormey*, CA-21076); Albany Medical College, NY (*G. R. Harper*, CA-06594); University of Rochester Cancer Center, NY (*Y.-C. Chang*, CA-11083); Northwestern University Medical Center, Chicago, IL (*J. D. Khandekar*, CA-17145); and University of Pretoria, South Africa (*G. Falkson*, CA-21692). The following institutions also participated in the study: Chicago Medical School, IL (CA-14144), and Tufts University, Walpole, MA (CA-07190).

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TABLE 1.—*Continued*

Characteristics	No. of patients
Response (ECOG criteria)†	
Complete or partial response	0
Disease progression	24
Refused further therapy due to neurologic toxicity *	4
Toxicity	
Leukopenia (≤ 3000 cells/μl)‡	1
Thrombocytopenia (≤ 100,000 cells/μl)‡	3
Phlebitis	4
Nausea and vomiting	7
Neurologic toxicity (ECOG grade)†	20
1	7
2	10
3	3
4	0

* Excludes 7 ineligible patients of 35 treated.

† *See* ref 6.

‡ Hematologic toxicity data available for 22 patients.

study. Median survival of the 28 evaluable patients was 120 days; median time to failure was 25.5 days. All but four patients have died. Toxicity was mild, except for neurologic symptoms in 20 patients which included lethargy, dizziness, paresthesias, anxiety, disorientation, agitation, and hallucinations. Four patients required a dose reduction; one of the four tolerated later dose escalation at a slower infusion rate. Two other patients were able to avoid a dose reduction after the iv rate was similarly reduced. Only four patients refused therapy due to toxicity. Thus, early failure was responsible for the fact that only four patients had an adequate trial of therapy (8 weeks).

This trial confirms the results reported from the Cancer and Leukemia Group B, in which no responses were observed in 30 evaluable patients using 80 mg/m^2 of drug three times per week (3). A survey of the literature reveals that only three of 86 patients with breast cancer have shown objective response (3,4). We conclude that spirogermanium has little activity in previously treated breast cancer.

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Phase II Evaluation of Doxorubicin Plus Bleomycin in Hepatocellular Carcinoma: A Southeastern Cancer Study Group Trial[1,2]

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The chemotherapy of primary cancer of the liver has generally been disappointing. Doxorubicin has produced the best systemic single-agent results (1). Tormey et al (2) achieved partial responses in three of three patients with hepatoma who were treated with doxorubicin and bleomycin; these results prompted our study.

Patients with incurable hepatocellular carcinoma were eligible if they had histologic proof of residual, recurrent, or metastatic carcinoma; had at least one measurable lesion; had recovered from previous myelosuppressive therapy; had not received previous doxorubicin or bleomycin; and gave written informed consent. Doxorubicin, 60 mg/m^2, was administered by iv injection once every 21 days. Bleomycin, 10 units/m^2, was given by iv injection twice weekly.

A partial response was defined as a decrease of $\geq$ 50% in the sum of the products of the diameters of measurable lesions and/or a reduction by 30% of the sum of the liver measurements below the costal margin in the case of hepatomegaly.

Of 60 patients entered, two were not eligible, three had inadequate data, one had a major protocol violation, one refused further treatment in the absence of toxicity, and one was lost to follow-up. Despite initial performance status ratings of 40%, 50%, and 60%, three patients died of rapid disease progression within the first week. Of 49 evaluable patients (table 1), eight (16%) achieved a partial response with a median duration of 12 months.

Toxicity was generally as expected and included granulocytopenia, nausea, vomiting, dermatitis, and stomatitis.

The response rate of 16% achieved with this drug combination in hepatocellular carcinoma is no better than that reported with doxorubicin alone (1,3); bleomycin added only toxicity. Alternative drugs and approaches (4,5) should be tested.

TABLE 1.—Patient characteristics

Characteristics	No. of patients
Median age in yrs (range): 58 (23-78)	
Karnofsky performance status	
100	4
70-90	32
40-60	13
Sex	
Male	40
Female	9
Prior therapy	
None	46
Radiotherapy	1
Chemotherapy	2
Response	
Partial	8
Stable	13
Progression	28
Median survival on study in wks (range): 10.6 (1-138)	
Toxic effect	
Granulocytopenia (< 1000 cells/μl)	18
Thrombocytopenia (< 25,000 cells/μl)	1
Drug death (infection)	1
Nausea/vomiting	26
Hypotension	1
Cardiovascular	1
Dermatitis	4
Oral	14

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Compilation of 1984 *Clinical Trials Summaries* published in *Cancer Treatment Reports*

Tumor	Drug	Dosage*	No. of evaluable patients	Response†	Page No.
Brain	Carmustine	220 mg/m² iv 6-8 hrs after surgery over 2-hr periods	21	NR	1505
	Carmustine + Baker's antifol	Carmustine: 40-50 mg/m²/day × 3 days Baker's antifol: 175-225 mg/m²/day × 3 days	16	7 PR	431
	PCNU	70-125 mg/m² by single 2-hr infusion q 6 wks	26	2 PR	441
	Vindesine	3 mg/m²/wk	16	NR	807
Breast	Cyclophosphamide + methotrexate + 5-FU + metoclopramide	Cyclophosphamide: 600 mg/m² by iv injection Methotrexate: 40 mg/m² by iv injection 5-FU: 600 mg/m² by iv injection Metoclopramide: 1-2 mg/kg diluted in 50 ml of 0.9% sodium chloride solution × 15 mins	40	NR	921
	Mitomycin	20-50 mg/m²/course by iv bolus	15	1 PR	805
	Mitoxantrone	4 mg/m²/day × 3 by iv infusion over 10 mins in 100 ml of D5W q 3 wks	34	2 PR	1511
	Spirogermanium	120 mg/m² by iv infusion in 150 ml of saline over 60-90 mins on Monday, Wednesday, and Friday of each wk	28	NR	1515
	Spirogermanium	180-250 mg/m² by continuous infusion 24 hrs/day × 5 days q 2 wks	17	NR	1197
	Vinblastine	1.6 mg/m²/day by constant infusion × 5 consecutive days for 3-4 wks	15	NR	803
Cervical	Amsacrine	30-40 mg/m² iv in 250 ml of D5W over 1 hr for 3 days q 21 days	20	NR	443
	Etoposide	100 mg/m² diluted in 150 ml of NS over 45 mins on Days 1, 3, and 5	19	1 PR	1513
Colorectal	Amsacrine	D5W by 1-hr iv infusion at 90 mg/m² q 3 wks	152	1 CR, 2 PR	929
	4-Demethoxydaunorubicin	12.5-15 mg/m² iv q 3 wks	43	1 PR	689
	4'-Epi-doxorubicin	90 mg/m² in 200 ml of D5W iv over 30 mins q 3 wks	39	NR	1507
	Mitolactol	100 mg/m²/day × 42 days	68	3 PR	1303
	Vindesine	3 mg/m² iv × 7 wks	16	1 CR	555
Endometrial adenocarcinoma	Tamoxifen	10-20 mg orally twice/day	24	NR	809
Gastric	Amsacrine	D5W by 1-hr infusion at 90 mg/m² q 3 wks	20	NR	929
Upper gastrointestinal tract	4-Demethoxydaunorubicin	10-15 mg/m² iv q 3 wks	25	1 PR	1415
Head and neck	Mitoguazone	500 mg/m² iv weekly	25	3 PR	1301
	PCNU	60-100 mg/m² as 1-hr infusion	29	NR	437
Epidermoid carcinoma	Bisantrene	260 mg/m² diluted to a volume of 500 ml of D5W iv over ≥ 60 mins	21	PR	687
Squamous cell carcinoma	Amsacrine	30-40 mg/m² iv × 3 consecutive days q 21 days	25	1 PR	435
	Gallium nitrate	700 mg/m² in 250 ml of NS over 30 mins q 2 wks	16	NR	1047
	Vindesine	3 mg/m² iv q 7 days	25	2 PR	559
Hepatocellular	Doxorubicin + bleomycin	Doxorubicin: 60 mg/m² iv q 21 days Bleomycin: 10 units/m² iv twice/wk	58	8 PR	1517
Hepatoma	Amsacrine	60-160 mg/m² q 3 wks	20	1 PR	923
Hodgkin's disease	PCNU	70-125 mg/m² divided into 5 daily infusions q 6 wks	7	2 CR	441
Lung					
Adenocarcinoma	Mitomycin + methotrexate + vincristine	Mitomycin: 17 mg/m² at 3-wk intervals Methotrexate: 30 mg/m² at 3-wk intervals Vincristine: 2 mg iv at 3-wk intervals	21	4 PR	1299
	Vindesine	3 mg/m²/wk by rapid iv infusion	15	1 PR	557
Bronchogenic carcinoma	Mitoxantrone	5 mg/m²/wk by 30-min iv infusion	141	2 PR	1295
Non-small cell	Bisantrene	260-280 mg/m² by iv infusion	15	NR	927
	4-Demethoxydaunorubicin	15 mg/m² by slow iv push q 3 wks	20	NR	563
	Doxorubicin	60-90 mg/m² by 6- and 24-hr continuous infusion q 3 wks	22	1 PR	681

Compilation of 1984 *Clinical Trials Summaries* published in *Cancer Treatment Reports* (continued)

Tumor	Drug	Dosage*	No. of evaluable patients	Response†	Page No.
	PALA + PCNU	PALA: 5 g/m^2 by iv infusion over 15–30 mins q 2 wks PCNU: 75–100 mg/m^2 by iv infusion over 30 mins q 6 wks	58	1 PR	1297
Small cell	Etoposide	125 mg/m^2 iv over 1 hr on Days 1, 3, and 5 q 3 wks	23	NR	1413
	Mitoguazone	400–600 mg/m^2 by iv infusion over 90 mins	22	NR	561
	Vindesine	3 mg/m^2/wk iv	20	1 PR	1407
Unspecified	Diaziguone	22.5 mg/m^2 iv over 10 mins once q 4–5 wks	40	NR	1193
Melanoma	Cisplatin + carmustine + dacarbazine + tamoxifen	Cisplatin: 25 mg/m^2/day iv for 3 days q 3 wks Carmustine: 150 mg/m^2 iv q 6 wks Dacarbazine: 220 mg/m^2/day iv for 3 days q 3 wks Tamoxifen: 10 mg orally twice/day	20	4 CR, 7 PR	1403
	4′-Epi-doxorubicin	75 mg/m^2 by slow iv injection over 5–10 mins in either NS or DW q 3 wks	15	NR	1509
	PCNU	75–100 mg/m^2 q 6 wks as 1-hr infusion	22	1 CR	1049
	Vindesine	1.5 mg/m^2/day by continuous iv infusion × 5 consecutive days	15	NR	1199
Myeloma	Chlorozotocin	120 mg/m^2 q 6 wks	55	NR	685
	Chlorozotocin + prednisone	Chlorozotocin: 120 mg/m^2 iv on Days 1–7 Prednisone: 75 mg orally on Days 1–7	22	NR	1409
Neuroblastoma	Amsacrine	60 mg/m^2/day iv × 5 consecutive days as a 60-min infusion and diluted to a vol of 300 ml/m^2 in D5W	20	NR	1051
Ovarian	Razoxane	1.5–2.5 g/m^2/wk orally divided into 3 doses on Day 1	21	NR	439
	Teniposide	100–150 mg/m^2 by 1- or 24-hr continuous infusion	20	NR	815
	Vinblastine	1.0–1.4 mg/m^2/24 hrs for 5 days iv in 500 ml of D5W	16	NR	1417
Pancreatic	Amsacrine	90–120 mg/m^2 q 21 days	31	NR	1411
	Amsacrine	90 mg/m^2 by 1-hr iv infusion in D5W	27	NR	929
	Metoprine	40–50 mg/m^2 orally q 2–3 wks	24	NR	1053
Prostatic	Etoposide	50 mg/m^2/day by continuous infusion × 5 days q 28 days	21	NR	1195
Renal	Diaziguone	27 mg/m^2 as 60-min infusion q 4 wks	29	1 PR	1055
Renal adenocarcinoma	Vinblastine	1.5 mg/m^2/day in 1000 ml of D5W given by continuous 24-hr infusion × 5 days q 4 wks	19	3 PR	925
Renal cell	PCNU	75–100 mg/m^2 q 6 wks as 1-hr infusion	34	1 PR	1049
	Spirogermanium	80 mg/m^2 by iv infusion for 1 hr 3 × wk for 2 wks, then twice/wk for 2 wks	36	NR	1305
Sarcoma	Methotrexate	40 mg/m^2 by iv push	21	NR	683
	Mitoxantrone	5 mg/m^2/wk iv over 30 mins	53	NR	813
Solid tumors	Mitomycin + metronidazole	Mitomycin: 20 mg/m^2 iv q 6 wks Metronidazole: 7 g/m^2 orally q 6 wks	16	1 PR‡	1191

*D5W = 5% dextrose in water; NS = normal saline; DW = dextrose in water.

†NR = no response; PR = partial response; CR = complete response.

‡Adenocarcinoma of unknown origin.

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1985 Fellowships in Brain Tumor Research

The Association for Brain Tumor Research (AFBTR), Chicago, is now accepting applications for fellowships from postdoctoral candidates whose intent is to pursue a career in brain tumor research. Preference will be given to physicians who are US citizens or permanent residents of the United States seeking research training that will enable them to pursue careers as clinical investigators.

AFBTR fellowships offer an award of $18,000 per annum plus a $2000 annual travel allowance for a period of 2 years, with a third-year renewable option. Each year's travel must include one presentation to the AFBTR Board of Directors in Chicago.

All applications will be reviewed by the Association's Medical Advisory Council, and Awards will be made on the basis of their recommendations. Criteria for selection will include the quality of the individual applicant; the quality of the program to which s/he is applying; and the research s/he is undertaking.

Applications must be submitted by the sponsoring program director, and deadline for completed applications is *January 4, 1985*. Awards will be announced by April 1, 1985 for fellowships to begin July 1, 1985.

Application forms may be obtained from the Association for Brain Tumor Research, Suite 200, 6232 N Pulaski Rd, Suite 200, Chicago, IL 60646, and completed applications should be mailed to the same address.

For further information, contact the AFBTR Executive Director, Donald Segal, at 312-641-5252.

Cancer of Women

Tampa, Florida, February 1–2, 1985

Among the topics in this 11th Annual Fred J. Woods Lecture Series are radiation and drug resistance of breast cancer, screening mammography, and the clinical use of clonogenic assay in breast and ovarian cancer. The series is sponsored by the St. Joseph's Hospital of Tampa Foundation, Inc, and the American Cancer Society, Hillsborough County Florida Unit; it meets the criteria for 10 hours of Category I credit. The registration fee is $50.

For further information, contact: Ralph Jensen, MD, St. Joseph's Hospital, PO Box 4227, Tampa, FL 33677 (telephone: 813-870-4016).

Second International Conference on the Modulation and Mediation of Cancer by Vitamins and Micronutrients

Tucson, Arizona, February 10–13, 1985

This conference will be held at the Arizona Health Sciences Center under the sponsorship of the Arizona Cancer Center. Dr. Frank L. Meyskens (University of Arizona) and Dr. Kedar N. Prasad (University of Colorado) will serve as cochairmen.

For further information, contact: Mary Humphrey, Conference Coordinator, Arizona Cancer Center, Tucson, AZ 85724 (telephone: 602-626-6044).

Oncology Seminar Series: Radiation Effects

Buffalo, New York, February 19, 1985

This session (5 CME credit hours) will be held in the Hilleboe Auditorium, Research Studies Center, Roswell Park Memorial Institute. The chairperson is Diane Cookfair, Ph.D.

For further information, contact: Ms. Gayle Bersani, Education Office, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263 (telephone: 716-845-2239).

Fourth Winter Symposium on Hematologic Malignancies

Snowbird, Utah, March 9–16, 1985

For information, contact: Dr. Stephen E. Jones, Section of Hematology and Oncology, University of Arizona Cancer Center, Tucson, AZ 85724 (telephone: 602-626-6372).

Current Cancer Research: Springboards for the Future

Chapel Hill, North Carolina, March 21–22, 1985

This ninth annual symposium marking the scientific dedication of the Lineberger Cancer Research Center of the University of North Carolina at Chapel Hill will feature the following speakers: Drs. S. Altman, S. Cohen, C. Croce, W. Eckhardt, R. Gallo, E. Kieff, A. Levine, M. Oldstone, P. Sharp, and R. Weinberg.

For further information, contact: Ms. Pam Upchurch, Lineberger Cancer Research Center, UNC-CH, Chapel Hill, NC 27514.

Diet and Human Carcinogenesis

Aarhus, Denmark, June 19–21, 1985

The aim of this Third Annual Symposium of the European Organization for Cooperation in Cancer Prevention Studies (ECP) is to present to the scientific and general communities a synopsis of the most recent knowledge regarding the epidemiologic and biologic aspects of diet as related to human carcinogenesis. The following topics will be covered: causal and protective agents in human carcinogenesis; diet and breast cancer; diet and digestive tract cancers; diet, cancer, and other diseases; role and feasibility of prospective and intervention studies on diet and cancer; and problems involved in dietary counseling.

The symposium will also include: a panel discussion on the dietary recommendations prepared in a joint IUNS (International Union of Nutritional Sciences) and ECP workshop; a seminar on the value of different methodologic approaches in epidemiologic studies on diet and cancer; and a poster session.

Participants are invited to present poster papers. Registered participants should send abstracts of their papers for review by the scientific committee no later than *April 15, 1985*. Abstracts should not exceed one 21 × 29.7-cm page (including authors' names, affiliations, and text).

For further information, contact: Mr. J. Geboers, Lic. Sc., Secretary-General, 3rd ECP Symposium, c/o Division of Epidemiology, Sint-Rafael University Hospital, Capucijnenvoer 33, B-3000 Leuven, Belgium.

Fourth World Conference on Lung Cancer

Toronto, Canada, August 25–30, 1985

An anticipated 2500 members of the international medico-scientific community with special interest in lung cancer will gather to share new ideas, research results, and experiences. Under the auspices of the International Association for the Study of Lung Cancer, the conference will be a combination of panels, symposia, lectures, workshops, ciné clinics, and exhibits.

Topics addressed will be prevention, epidemiology, respiratory carcinogenesis, early diagnosis and staging pathology, surgery, radiotherapy, chemotherapy, immunotherapy, cellular kinetics, tumor markers, and imaging. The site of the sessions and exhibits will be the Metro Toronto Convention Center.

For further information, contact: Dr. Ronald Feld, Secretary General, The IV World Conference on Lung Cancer, c/o Secretariat Office, 342 MacLaren St, Ottawa, Ontario, Canada K2P OM6.

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